KJU
Korean Journal of Urology

www.kjurology.org
http://dx.doi.org/10.4111/kju.2014.55.12.828

Original Article - Pediatric Urology

Efficacy, Tolerability, and Safety of Oxybutynin Chloride in Pediatric Neurogenic Bladder With Spinal Dysraphism: A Retrospective, Multicenter, Observational Study

Jung Hoon Lee, Kyoung Rok Kim, Yong Seung Lee[1], Sang Won Han[1], Kun Suk Kim[2], Sang Hoon Song[2], Minki Baek[3], Kwanjin Park[4]

Department of Urology, Seoul National University College of Medicine, Seoul, [1]Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, [2]Department of Urology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, [3]Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, [4]Division of Pediatric Urology, Department of Urology, Seoul National University Childrens' Hospital, Seoul National University College of Medicine, Seoul, Korea

Purpose: Anticholinergics are a key element in treating neurogenic detrusor overactivity, but only limited data are available in the pediatric population, thus limiting the application to children even for oxybutynin chloride (OC), a prototype drug. This retrospective study was designed to provide data regarding the efficacy, tolerability, and safety of OC in the pediatric population (0–15 years old) with spinal dysraphism (SD).

Materials and Methods: Records relevant to OC use for neurogenic bladder were gathered and scrutinized from four specialized clinics for pediatric urology. The primary efficacy outcomes were maximal cystometric capacity (MCC) and end filling pressure (EFP). Data on tolerability, compliance, and adverse events (AEs) were also analyzed.

Results: Of the 121 patient records analyzed, 41 patients (34%) received OC at less than 5 years of age. The range of prescribed doses varied from 3 to 24 mg/d. The median treatment duration was 19 months (range, 0.3–111 months). Significant improvement of both primary efficacy outcomes was noted following OC treatment. MCC increased about 8% even after adjustment for age-related increases in MCC. Likewise, mean EFP was reduced from 33 to 21 cm H_2O. More than 80% of patients showed compliance above 70%, and approximately 50% of patients used OC for more than 1 year. No serious AEs were reported; constipation and facial flushing consisted of the major AEs.

Conclusions: OC is safe and efficacious in treating pediatric neurogenic bladder associated with SD. The drug is also tolerable and the safety profile suggests that adjustment of dosage for age may not be strictly observed.

Keywords: *Child; Neurogenic urinary bladder; Oxybutynin*

Article History:
received 29 August, 2014
accepted 15 October, 2014

Corresponding Author:
Kwanjin Park
Department of Urology, Seoul National University College of Medicine, 103 Daehak-ro, Jongno-gu, Seoul 110-799, Korea
TEL: +82-2-2072-0695
FAX: +82-2-742-4665
E-mail: urodori@naver.com

INTRODUCTION

About 0.6 to 4 newborn children per 1,000 suffer from spinal dysraphism (SD). This can be characterized by incomplete development of the central nervous system, which includes open (myelocele and meningomyocele) or closed (lipoma, occult spina bifida, and dermal sinus) entities [1,2]. Frequently, the above-mentioned anomalies are complicated by neurogenic bladder dysfunction and detrusor-sphincter dysfunction, represented by urinary incontinence, urinary tract infection, and deterioration of the upper urinary tract [3,4]. Clean intermittent catheterization and anticholinergic drugs have been accepted as conservative measures to alleviate these problems [5].

Anticholinergic agents inhibit the binding of acetylcholine to the cholinergic receptors (thereby inhibiting in-

voluntary bladder contractions), increase the volume at which the first involuntary bladder contraction occurs, reduce intravesical pressure, and may increase total bladder capacity [6-8]. Common safety concerns for anticholinergic drugs relate to decreased secretory function (dry mouth, constipation), reduced smooth muscle contraction (constipation and acute urinary retention), and untoward effects on the central nervous system.

Recent years have seen several newly developed anticholinergics be applied for the treatment of neuropathic bladder. However, most data were focused on the treatment of adults and only a small number of data are available for children. So far, oxybutynin, tolterodine, propiverine, and solifenacin have been applied to children, but not often enough to warrant their use in terms of safety and efficacy. In Korea, only oxybutynin is accepted for children over 5 years of age, thus limiting the choice for adequate anticholinergics for children. Thus, more evidence in children should be obtained to loosen the restrictions on anticholinergic use. Thus, we analyzed our data on the long-term safety, tolerability, and efficacy of oxybutynin chloride (OC) in children with SD to provide more information for the current database.

MATERIALS AND METHODS

The terminology and definitions in this paper comply with the 2006 standardization report of the International Children's Continence Society [9]. After obtaining permission from the Ethical Review Board, four institutions took part in this study, all of which have multidisciplinary teams for children with SD. These children are seen on regular basis depending on age and clinical course, but at least once yearly. The patient database was scrutinized for children and adolescents meeting the selection criteria of having neurogenic detrusor overactivity due to SD, having been allocated to treatment with oxybutynin, and having been prescribed oxybutynin at less than 15 years of age. In all patients, the diagnosis of neurogenic detrusor overactivity had been proven by history and urodynamic assessment. Detrusor overactivity was defined as uninhibited detrusor contractions of 15 cm H_2O or greater. Intermittent catheterization was performed in those who showed dyssynergic sphincter.

The primary efficacy outcome parameters, maximal cystometric capacity (MCC) and end filling pressure (EFP), i.e., peak detrusor pressure at capacity, were evaluated before and during OC treatment. With regard to MCC, effects subsequent to OC treatment and effects attributable to the age-related increase in capacity had to be adjusted for. Therefore, the individual MCC was calculated as a percentage of expected age-adjusted capacity according to the formula proposed by Hjalmas [10].

The second efficacy parameters were the compliance assessed during cystometry and the number of incontinence episodes assessed from the information given by the parents and their caregivers. While the reference value was defined before OC medication, during-treatment values were assessed at the last available urodynamic investigation during OC treatment. Thus, the conditions and time intervals between reference and during treatment varied widely in each patient.

Other important variables during long-term treatment were tolerability, compliance, and safety issues. We measured total days of OC treatment and compliance when relevant data were available. Adverse events (AEs), mentioned in the patient's file or reported by patients or their caregivers during the follow-up visits, were also documented.

For statistical analysis of the efficacy and safety parameters, the paired t-test and chi-square test were applied. The level of statistical significance was set at p=0.05.

RESULTS

Owing to the retrospective nature of this observational, uncontrolled study, some data for the different parameters were missing to various extents. Of the 385 files for pedia-

TABLE 1. Demographics and clinical data of study population

Parameter	Value
Spinal dysraphism	
Open (myelocele and meningomyelocele)	39 (32)
Closed (occult spina bifida including spinal lipoma)	82 (68)
Sex	
Male	58 (48)
Female	63 (52)
Age at treatment with OC (y)	
0–5	41 (34)
6–10	37 (31)
11–15	43 (35)
Median (range)	8 (1–15)
Pretreatment urodynamic diagnosis	
Detrusor overactivity with synergic urethra	16 (13)
Detrusor overactivity with dyssynergic urethra	105 (87)
Final prescribed dosage (mg/d)	
3–5	4 (3)
5–10	89 (74)
11–15	19 (16)
>15	9 (7)
Updosing	20 (17)
Duration of drug treatment	
<3 mo	12 (10)
3 mo–1 yr	42 (35)
1–3 yr	39 (32)
>3 yr	28 (23)
Median (range)	19 (0.3–111)
Compliance (%)	
<50	4 (3)
50–70	16 (13)
70–100	101 (84)

Values are presented as number (%) unless otherwise indicated.
OC, oxybutynin chloride.

tric patients, 121 files of neurogenic detrusor overactivity owing to SD were eligible for review (87 in center one, 22 in center two, 4 in center three, and 8 in center four). No significant differences in demographic data were noted between those who were included and those who were excluded from this study. The demographic data and clinical parameters of the patients are given in Table 1. A larger number of closed SD cases than the open type were included. The median age at treatment was 8 years (range, 1–15 years). Forty-one patients (34%) received OC at less than 5 years of age.

OC was prescribed as a first anticholinergic treatment in all patients. Also, it was confirmed that no medication or treatment other than OC was given for sphincter or detrusor function before or during treatment. The prescribed dose of OC was adjusted individually at the discretion of investigators and varied from 3 to 24 mg/d.

Although patients who were not able to swallow the tablet were treated with immediate-release OC prescribed into syrup, those over 5 years of age who were able to swallow the tablet were prescribed the extended-release form of OC (5–15 mg/d). Whereas 69 patients (57%) used less than 5 mg of OC, 50 patients (41%) used at least 10 mg of OC a day. Up-dosing was reported in 20 patients (17%) owing to insufficient efficacy. The median treatment duration was 19 months (range, 0.3–111 months).

1. Efficacy

The primary urodynamic parameters, MCC and EFP, were improved significantly following OC treatment (Fig. 1). This improvement in MCC was maintained even after we adjusted for age-related increases in bladder capacity. The mean percentages of the expected age-adjusted capacities were still significantly increased by 8% (Wilcoxon singed rank test) even after this adjustment. Compared to pretreatment values, 65 (53%) and 31 (26%) achieved improvement and normalization of adjusted bladder capacity, respectively, following OC treatment.

Mean pretreatment EFP was 33 cm H_2O, and 51 patients (42%) showed a mean EFP of more than 40 cm H_2O. Following treatment, mean EFP was reduced to 21 cm H_2O and in 19 patients (16%) the value was still more than 40 cm H_2O.

As secondary efficacy parameters, bladder compliance and global assessment of incontinence were compared (Fig. 2). A significant increase in bladder compliance was seen after OC treatment. OC markedly improved the control of incontinence. Approximately 90% reported that the medication helped the control of incontinence.

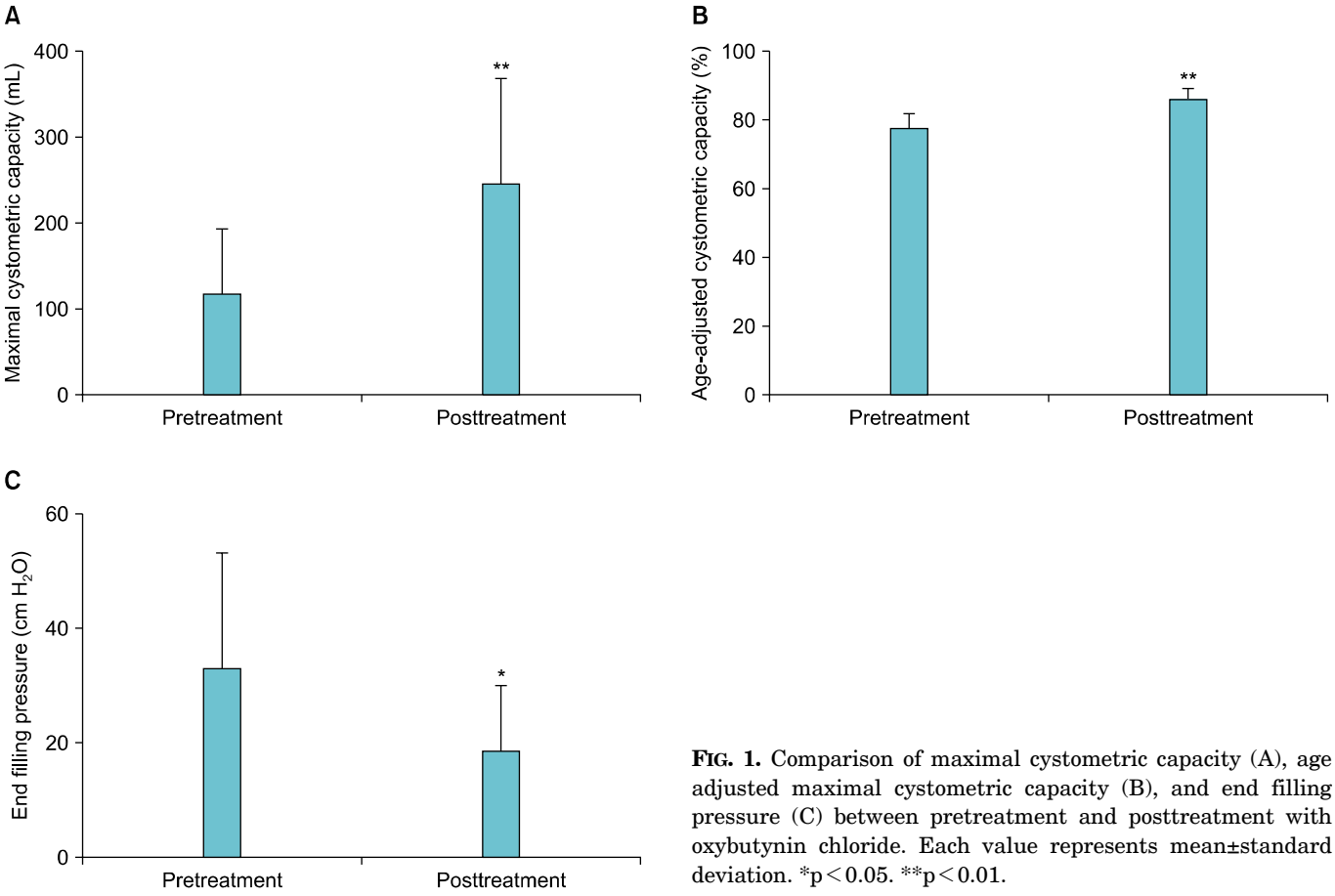

FIG. 1. Comparison of maximal cystometric capacity (A), age adjusted maximal cystometric capacity (B), and end filling pressure (C) between pretreatment and posttreatment with oxybutynin chloride. Each value represents mean±standard deviation. *$p<0.05$. **$p<0.01$.

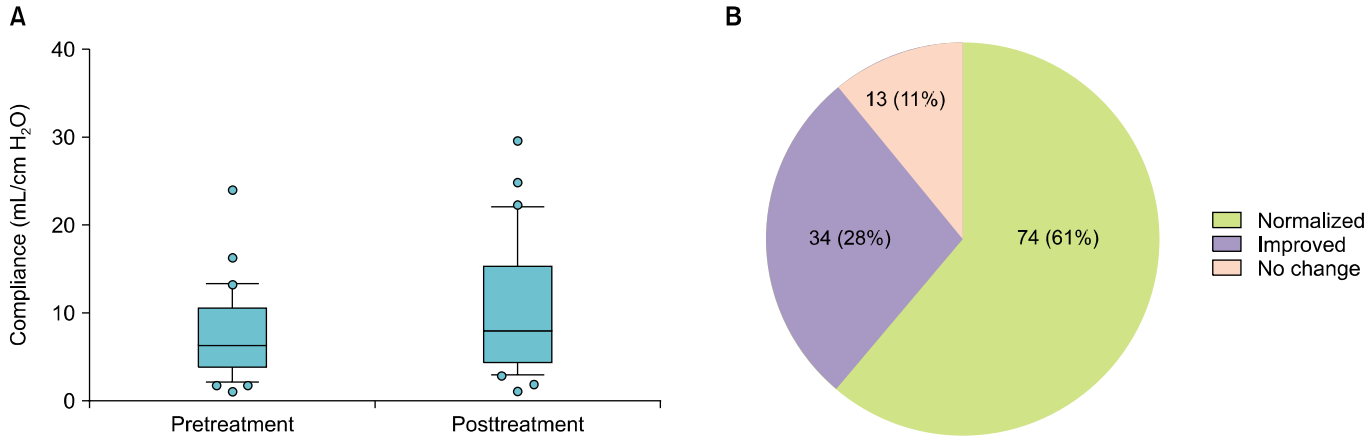

FIG. 2. The second efficacy parameters are depicted. Changes of bladder compliance (A) and incontinence status following the treatment of oxybutynin chloride (B) are seen.

TABLE 2. Adverse events occurred following medication with oxybutynin chloride

Adverse events	No. (%)	Severity (n)	No. of leading to discontinuation (%)
Dry mouth	1 (1)	Mild (1)	-
Constipation	8 (7)	Mild (5), moderate (3)	4 (3)
Poor feeding	1 (1)	Mild (1)	-
Facial flushing	4 (3)	Mild (3), moderate (1)	-
Voiding difficulty	1 (1)	Mild (1)	-
Drowsiness	2 (2)	Mild (2)	2 (2)

2. Tolerability and safety

Overall compliance for OC was good; 101 patients (82%) showed more than 70% compliance. OC was tolerable in most patients. The mean duration of treatment with OC was 576 days (range, 30–3,330 days). Only 22 patients (18%) took OC for less than 90 days and approximately 50% of patients used OC for more than 1 year. OC was taken for more than 3 years in 20 patients (17%). Of those who discontinued the OC in less than 90 days, inadequate treatment response and AEs were responsible for early discontinuation in 16 (72%) and 6 patients (28%), respectively.

The reported AEs are described in Table 2. No AEs were seen in 104 patients (85%). Constipation and facial flushing consisted of the major AEs. Of the 6 AEs that led to discontinuation of OC, constipation was responsible in 4 cases and dizziness in 2. No serious AEs were documented.

DISCUSSION

In this study, we collected and analyzed data from several large institutions in Korea to demonstrate the efficacy, tolerability, and safety of OC in pediatric patients with SD. Although the limited number of patients in our data set prevented us from drawing definite conclusions about efficacy and safety, our data revealed that OC was efficacious, safe, and tolerable in pediatric patients, as in adults. Of note, the fact that about one-third of the patients treated with OC were less than 5 years of age suggested that OC may be tolerable and safe at these ages for which the use of OC is not approved. This is consistent with a previous report showing good efficacy profiles in children aged less than 5 years without any increase in AEs [11].

OC was the first anticholinergic used in all patients. This was because no anticholinergics other than OC are approved for use in the pediatric population in Korea. Because our data demonstrated the benefit and safety of OC in children, it is expected that other anticholinergics may also be useful in children. Previous studies have already shown the efficacy and safety of other anticholinergics such as tolterodine [12] and propiverine [8].

One interesting finding that should be mentioned was that the dosages used were comparable to those for adults. Ninety percent of treated patients received 5 to 15 mg of OC, which is comparable to the 86.5% reported previously for Korean adults [13]. Although this study was conducted in patients with neurogenic bladder, which often requires higher doses of anticholinergics for treatment than does the nonneurogenic type [14], the finding that higher dosages of OC can be used in children may be additional supporting evidence for the tolerability and safety of OC in the pediatric population. This is consistent with the claim that comparatively high doses of anticholinergics can be used in children [15].

Like previous reports of OC in the pediatric population, the clinical efficacy of OC in neurogenic detrusor overactivity was documented in this study by significant improvements in all primary efficacy outcome parameters. In particular, MCC was increased even after adjustment for the age-related physiological increase. The effects attributed to OC, which were calculated following adjustment for the age-related increase in bladder capacity, demonstrated a significant increase of 8%. We believe that this increase is meaningful given the fact that the normal values for bladder capacity were set from the data of healthy controls of

the same age [10]. Consequently, about one-half and one-third of the patients achieved improved and normalized bladder capacity following treatment, respectively.

Reduction of EFP is expected to preserve the upper urinary tract with regard to renal insufficiency. Following treatment with OC, mean EFP decreased and about 30% of patients with an EFP over 40 cm H_2O before treatment experienced the conversion of their EFP into the safe range.

About 90% of patients reported that their incontinence improved after treatment, but only 38% reported complete control. Because OC improved incontinence by reducing detrusor overactivity and increasing compliance, this improvement was not unexpected. The failure of complete control of incontinence may be related to inadequate dosing, the concomitant presence of sphincteric incompetence, or an insufficient number of OC to control incontinence.

We believe that tolerance reflects the real-world status of drug safety, although other reasons may affect it. Over 80% showed good tolerance and about one-half of the patients took OC for more than 1 year, which is comparable to the tolerance profile reported in adults.

The main concern for use of anticholinergics in pediatric populations is a higher occurrence of AEs in children and more severe AEs than in adults and the possible occurrence of side effects related to the central nervous system. Our data contradicted this concern. Constipation and facial flushing of mild to moderate severity were the main side effects of OC in treated children. Because constipation is inherent to this population owing to the neurogenic bowel problem, a much small number was affected by constipation attributed to OC. Only facial flushing was the main AE from OC use. Compared with the high incidence of dry mouth in adults, no significant episode was realized [16]. The occurrence of AEs likely to be related to the central nervous system consisted of only 2 cases of dizziness. Although the severity was not reported to be significant, this led these patients to quit the medication. Assuming that the low incidence of AEs may be related to insufficient inquiry in the real-world situation, it would be safe to say that OC was acceptable in pediatric neurogenic bladder with SD. Also, our data may help to expand the indication for OC in children and prompt more studies of anticholinergics in children for their approval in Korea. Despite the availability of several anticholinergics for the adult population, only OC is approved in children over 5 years of age in Korea, thus limiting the beneficial effect of anticholinergics in children. The necessity for expanding the indication for anticholinergics was reflected by the unequal distribution of enrolled patients with regard to each hospital. Although all four hospitals were believed to have a comparable number of patients with SD, the enrolled number for each hospital was quite different, implying a lower preference for OC in the clinical practices of some centers. These practices seem to have treated the patients with other anticholinergics by off-label use, realizing the limitation of OC in treating this kind of patient. The fact that the main reason for quitting OC was insufficient response rather than AEs should be born in mind. In this regard, increased use of anticholinergics other than OC to achieve better response in real practice is a natural tendency for clinicians despite the risk of off-label use.

The limitations of this study should be mentioned. This was an observational, retrospective, and descriptive study without a control group. As a result, the efficacy and safety of each patient was not measured on the same time scale, precluding drawing definite conclusions. This explained why we did not analyze the data in the voiding diaries. In addition, a substantial number of patients were excluded from this study owing to a lack of comparable urodynamic data, which is inherent in a retrospective, real-world clinical study.

An additional potentially significant limitation is that we did not check the presence of constipation. However, we were not able to examine this owing to the retrospective nature of our study and the lack of an effective diagnostic tool. Although the population treated with OC was not small, the wide age range may not allow us to obtain sufficient information regarding safety for all age ranges. Nonetheless, the large number of patients, the multicenter design, and the detailed information on tolerability may add valuable information to our current knowledge for the widespread use of OC.

CONCLUSIONS

This retrospective observational study showed that OC is safe and efficacious in treating pediatric neurogenic bladder caused by SD. The drug is also tolerable and the safety profile was not worrisome on the basis of the prevalence and severity of reported AEs.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

ACKNOWLEDGMENTS

This research was supported by a grant (12172MFDS231) from Ministry of Food and Drug safety in 2012.

REFERENCES

1. Bauer SB, Hallett M, Khoshbin S, Lebowitz RL, Winston KR, Gibson S, et al. Predictive value of urodynamic evaluation in newborns with myelodysplasia. JAMA 1984;252:650-2.
2. Copp AJ, Stanier P, Greene ND. Neural tube defects: recent advances, unsolved questions, and controversies. Lancet Neurol 2013;12:799-810.
3. Mourtzinos A, Stoffel JT. Management goals for the spina bifida neurogenic bladder: a review from infancy to adulthood. Urol Clin North Am 2010;37:527-35.
4. Frimberger D, Cheng E, Kropp BP. The current management of the neurogenic bladder in children with spina bifida. Pediatr Clin North Am 2012;59:757-67.
5. Edelstein RA, Bauer SB, Kelly MD, Darbey MM, Peters CA, Atala A, et al. The long-term urological response of neonates with myelodysplasia treated proactively with intermittent catheterization

and anticholinergic therapy. J Urol 1995;154:1500-4.
6. Goessl C, Knispel HH, Fiedler U, Harle B, Steffen-Wilke K, Miller K. Urodynamic effects of oral oxybutynin chloride in children with myelomeningocele and detrusor hyperreflexia. Urology 1998;51:94-8.
7. Cartwright PC, Coplen DE, Kogan BA, Volinn W, Finan E, Hoel G. Efficacy and safety of transdermal and oral oxybutynin in children with neurogenic detrusor overactivity. J Urol 2009;182:1548-54.
8. Grigoleit U, Murtz G, Laschke S, Schuldt M, Goepel M, Kramer G, et al. Efficacy, tolerability and safety of propiverine hydrochloride in children and adolescents with congenital or traumatic neurogenic detrusor overactivity: a retrospective study. Eur Urol 2006;49:1114-20.
9. Neveus T, von Gontard A, Hoebeke P, Hjalmas K, Bauer S, Bower W, et al. The standardization of terminology of lower urinary tract function in children and adolescents: report from the Standardisation Committee of the International Children's Continence Society. J Urol 2006;176:314-24.
10. Hjalmas K. Urodynamics in normal infants and children. Scand J Urol Nephrol Suppl 1988;114:20-7.
11. Franco I, Horowitz M, Grady R, Adams RC, de Jong TP, Lindert K, et al. Efficacy and safety of oxybutynin in children with detrusor hyperreflexia secondary to neurogenic bladder dysfunction. J Urol 2005;173:221-5.
12. Ellsworth PI, Borgstein NG, Nijman RJ, Reddy PP. Use of tolterodine in children with neurogenic detrusor overactivity: relationship between dose and urodynamic response. J Urol 2005;174(4 Pt 2):1647-51.
13. Yoo DS, Han JY, Lee KS, Choo MS. Prescription pattern of oxybutynin ER in patients with overactive bladder in real life practice: a multicentre, open-label, prospective observational study. Int J Clin Pract 2012;66:132-8.
14. Bennett N, O'Leary M, Patel AS, Xavier M, Erickson JR, Chancellor MB. Can higher doses of oxybutynin improve efficacy in neurogenic bladder? J Urol 2004;171(2 Pt 1):749-51.
15. Bolduc S, Moore K, Lebel S, Lamontagne P, Hamel M. Double anticholinergic therapy for refractory overactive bladder. J Urol 2009;182(4 Suppl):2033-8.
16. Madhuvrata P, Singh M, Hasafa Z, Abdel-Fattah M. Anticholinergic drugs for adult neurogenic detrusor overactivity: a systematic review and meta-analysis. Eur Urol 2012;62:816-30.