The effectiveness of intravesical oxybutynin in the management of overactive bladder: a clinical study

Shoeb Alahmad,[1] Rawaa AlKayali,[2] Lubana Alkhoder,[3] Gihad Allugamie[4]

[1]Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Watanyia Private University, Hama; [2]Department of Biochemistry and Microbiology, Faculty of Pharmacy, Aleppo University; [3]Department of Laboratory Diagnosis, Faculty of Pharmacy, Al-Watanyia Private University, Hama; [4]Department of Urology, Hama Hospital, Ministry of Health, Hama, Syria

Correspondence: Shoeb Alahmad, Department of Pharmaceutical Analytical Chemistry, Faculty of Pharmacy, Al-Watanyia Private University, Hama, Syria.
Tel.: 00963988596094.
E-mail: shuaib.ahmad@wpu.edu.sy

Key words: overactive bladder, oxybutynin hydrochloride, intravesical administration, urinary catheterization, antimuscarinic.

Contributions: all the authors made a substantial intellectual contribution, read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: the authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: this study was approved by the Scientific Research Ethics Committee at the Faculty of Pharmacy, Al-Wataniya University (Ethics Approval No. 2574). And Hama Medical Center hospital gave approval for the study to review and publish information from the patient's records. The patients/participants provided their written informed consent to participate in this study.
The study was performed according to the principles outlined in the Declaration of Helsiniki.

Patient consent for publication: not applicable. Confidentiality was guaranteed by avoiding personal information from participants and using coding.

Funding: none.

Availability of data and materials: data and materials are available from the corresponding author upon request.

Acknowledgments: the authors would like to thank Joud Kaed and Kinana Allugamie for their assistance in conducting the research.

Received: 10 March 2024.
Accepted: 31 October 2024.

Urogynaecologia 2024; 36:328
doi:10.4081/uij.2024.328

Abstract

Overactive bladder (OAB) syndrome is a chronic, debilitating disorder with physical, psychological, and social repercussions that considerably reduces the quality of life for 12-17% of the population. Despite the emergence of novel antimuscarinic medicines, many OAB syndrome patients are unable to tolerate or respond to oral treatment. Oxybutynin hydrochloride (OH) is one of the most essential medications available. The purpose of this article is to investigate the efficacy of intravesical OH in treating patients with OAB who are unresponsive to oral medication or who experience intolerable systemic side effects of anticholinergic drugs.

OH was administered intravesically to 48 patients with neurogenic bladder and incontinence more than 8 times a day. Treatment consisted of dissolving 5 mg OH tablets in sterile saline, 40 mL, once a week. The duration of intravesical treatment with OH was applied once a week for 4 weeks. The rate of improvement was remarkable, and the best response was 70% in all 48 patients. Cystometrography was performed and revealed that cystocapacity before and after the initial modified intravesical oxybutynin was 123.41±24.83 and 308.08±30.68, respectively. One patient complained of slight pain in the lower abdomen, but this effect gradually subsided as treatment continued. The patient continued the entire treatment with four doses. These encouraging results indicate that intravesical instillation of OH is an attractive, effective, and safe alternative therapy in patients with neurogenic bladder who either do not respond or have intolerable side effects from oral medications.

Introduction

A considerable portion of the population suffers from the chronic medical illness known as overactive bladder (OAB) syndrome, which has a profound impact on their quality of life.[1] While it is more prevalent in people over the age of 40, it can also impact young people and children.[2] OAB significantly impairs quality of life; it affects social, emotional, sexual, vocational, and physical facets of day-to-day living.[3]

The definition of OAB has changed significantly throughout time. Right now, the 2014 definition provided by the International Consultation on Incontinence Research Society is the most precise and widely recognized worldwide: "overactive bladder syndrome is characterized by urinary urgency, with or without urgency urinary incontinence, usually with increased daytime frequency and nocturia, if there is no proven infection or other obvious pathology".[4] Over the past few years, oxybutynin hydrochloride (OH) has been the standard anticholinergic medication used to treat OAB.[5] Anticholinergic medications decrease bladder contractility, lower internal pressure in the bladder, inhibit postganglionic muscarinic

receptors, and raise the threshold for the ability to urinate.[6,7]

Oxybutynin chloride is a tertiary amine that has antimuscarinic, antispasmodic, and local analgesic effects. Right now, it can be purchased as a transdermal, extended-release, or immediate-release preparation. Many patients find oxybutynin's anticholinergic effects difficult to endure, even with the more recent extended-release and transdermal options.[8] In clinical practice, very few patients currently insist on taking anticholinergic medications for longer than six months.[9] Furthermore, even though OH is used at the highest possible dose to treat overactive detrusors, there may not be an adequate clinical response, or adverse effects (such as dry mouth or eyes, constipation, blurred vision, decreased sweating, or sleepiness) may arise that hinder the effectiveness of the medication.[10,11]

One of the biggest challenges to effectively managing OAB remains drug persistence or compliance. As a result, a novel approach and concept are desperately needed to address the issues with the way OAB is currently being treated clinically.[12]

According to recent reports, intravesical oxybutynin chloride is a successful treatment for neurogenic bladder dysfunction.[13,14,15] This treatment has a beneficial impact on urodynamic parameters and improves patient symptomatology.[16] Intravesical administration of oxybutynin can result in serum oxybutynin levels up to 10 times higher than oral administration but with fewer side effects because it avoids the presystemic metabolism of oxybutynin in the intestine and liver and lowers the concentration of the metabolite N-Desethyl-Oxybutynin (N-DEO).[17]

Therefore, the purpose of this research was to study the efficacy and safety of using intravesical OH in patients with overactive detrusors who were unresponsive to oral anticholinergic therapy.

Materials and Methods

Patients

The study protocol was approved by the Scientific Research Ethics Committee at the Faculty of Pharmacy, Al-Wataniya Private University.

The eligibility criteria were as follows: 48 patients attending the Urology and Reproductive Surgery Unit at Hama Medical Center Hospital, with a confirmed diagnosis of unknown reason OAB (urinary incontinence more than 8 times a day) and unresponsive to oral oxybutynin therapy (5 mg Oxybutynin Hydrochloride tablets for a month) or suffered from many intolerable side effects, which led to stopping treatment, including dry mouth, constipation, dry eyes, palpitations, dizziness, and drowsiness. Therefore, patients were transferred to another line of treatment alternative to the oral route using oxybutynin injected into the bladder.

Patients were classified into two groups (10 males and 38 females), and their ages ranged from 40 to 60 years (on average 51 years). The period of complaints in these patients ranges from a month to a year and a half (an average of nine months). The presence of urinary residue (ultrasound), and urinary tract infection represented the exclusion criteria.

Instillation of intravesical oxybutynin

The injection solution was prepared in sterile conditions. We used a solution of OH tablets that were crushed and dissolved in sterile saline (5 mg/40 mL) and adjusted the pH value of the solution to 5.86. These solutions were prepared by the pharmacy department of our institution. The solution was sterilized using a syringe filter: it usually consists of a plastic casing with a membrane filter with a pore size of 0.02 microns attached to the syringe. The liquid is drawn into a syringe and then passed through the filter to remove any other particles or microorganisms that may be present in the solution.

The 40 mL solution is then injected once (bolus) into the bladder *via* the Nelaton sonde. Immediately after urination or by clean intermittent catheterization and after ensuring (by echo) that the bladder was completely empty. The treatment was applied once a week for 4 weeks.

Evaluation

Physical examination includes an abdominal examination, digital rectal examination of the prostate in males, and vaginal examination in women. These assessments include an abdominal examination for scars, masses such as uterine fibroids, hernias, and distension of the bladder. A neurological screen for upper motor lesions such as Parkinson's disease, and a neurological screen for lower motor lesions, such as sacral-nerve root lesions, were performed. A direct rectal examination was done to determine the anal sphincter tone. Fecal impaction distends the distal sigmoid and rectum, resulting in inadequate detrusor activity and compromised bladder emptying. A vaginal examination reveals a prolapse of pelvic organs.

Three days of a bladder diary provide a stable and reliable measurement of the frequency of incontinent episodes. OAB sufferers may have urgency, frequency (more than eight voids per 24 hours), or nocturia (one or more voids after falling asleep and a return to sleep after voiding), with or without urge incontinence.

Laboratory tests include urine analysis and urinary culture to rule out other associated pathologies that may cause OAB□type symptoms (especially urinary tract infection and hematuria).

Symptom questionnaires are used to highlight the impact of the condition on quality of life and to determine whether or not the patient should undergo treatment.

Upper urinary tract evaluation with ultrasound, cystoscopic evaluation of the lower urinary tract and urodynamic study are also performed. All patients had undergone urodynamic testing, including cystometrography (CMG), if possible, with electromyography of the external urethral sphincter, measurement of single voided volume and residual urine volume, and uroflowmetry to establish the diagnosis of OAB by using room-temperature sterile physiological serum that was filled through the urodynamic catheter at rate of 50 mL/minute.

Results

According to the study design scheme, the symptoms were evaluated before treatment and after 4 weeks of oxybutynin bladder instillation by the urinary tenesmus, pain during urination, and the frequency of urination day and night based on the daily urination schedule. Patients were classified according to the response evaluation (Table 1 and Figure 1).

The changes in pretreatment nocturnal urinations frequency and after 4 weeks of intravesical oxybutynin were assessed in patients and the results are shown in Table 2. The mean of nocturnal urination frequency of female and male patients decreased ($p=0.028$ and $p=0.028$, respectively) (Figure 2).

The CMG data are shown in Table 3. Before the treatment, all patients demonstrated uninhibited contractions, and bladder capacity was 123.41±24.83 mL. Just 4 weeks after the initial treatment, bladder capacity was significantly increased (308.08±30.68 mL) (Figure 3).

Compared to the bothersome side effects that all patients previously experienced while on oral oxybutynin therapy, all oxybutynin side effects disappeared.

With the pH value of the solution adjusted to 5.86, no negative effect appeared with this treatment. One female patient complained of slight pain in the lower abdomen during the instillation of the first dose only, but this side effect gradually subsided as the instillation continued, and the patient continued the entire treatment with four doses.

Discussion

The most common parasympatholytic medicine used in urology is oxybutynin, which reduces bladder muscle spasms to treat urinary and bladder dysfunction, including frequent urination and the inability to control urination. It opposes the muscarinic acetylcholine receptor subtypes M1, M2, and M3 in a competitively antagonistic manner. In addition, at high doses, it acts as a calcium antagonist and a local anesthetic with direct spasmolytic actions on bladder smooth muscle.[18]

In this study, the effects of intravesical oxybutynin treatment on patients who did not respond to oral medication and who experienced intolerable systemic side effects from oral anticholinergic drugs were investigated.

This pilot study demonstrates that the positive clinical effect of OH was unchanged, and no side effects were observed. The improvement and better response rate were 84.2% in females and 40% in males. In different trials, the rate of symptomatic improvement has varied from 55% to 90%,[19] which clarifies that oxybutynin is quickly absorbed when injected into the bladder, producing noticeably higher plasma concentrations than when taken orally. Its direct binding to the cholinergic receptors found in the bladder's inner wall results in both the intended therapeutic efficacy and a quick response. Furthermore, the gastrointestinal tract and central nervous system muscarinic receptors are particularly sensitive to oxybutynin.[17,20]

Regarding the fact that the experiment was more successful in females than in males, this may be explained by the fact that the prostate, an external mechanical element in males, interacts with the bladder through a complicated system that reduces the responsiveness to therapy.

Furthermore, despite the high plasma concentrations, the current investigation verified that systemic side effects disappeared. This can be explained by the fact that oxybutynin when taken orally, travels *via* a first-pass hepatic process and is broken down into various metabolites by the cytochrome P450 (CYP3A4) system.[17,20]

The primary metabolite, N-DEO, has similar pharmacological properties to the parent compound but occurs in much higher concentrations after oral administration, and the N-DEO metabolite is

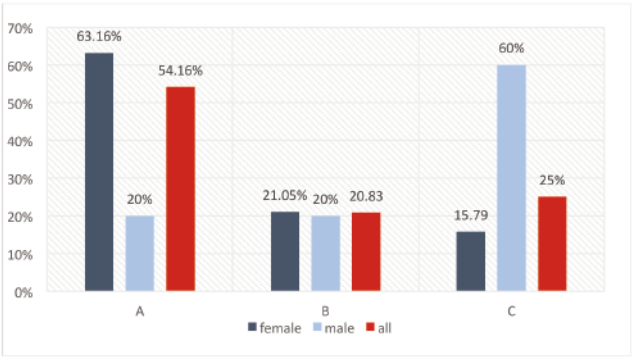

Figure 1. Patients' classification according to the response evaluation.

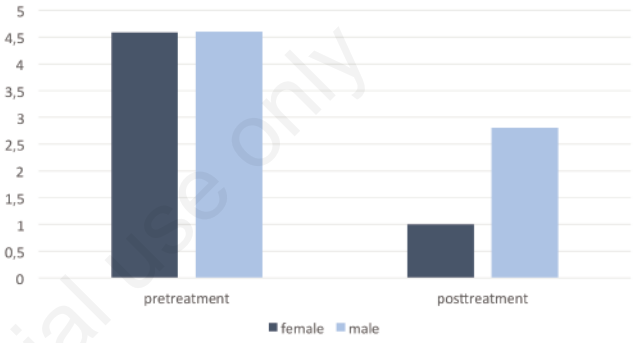

Figure 2. Nocturnal urination frequency before and after treatment.

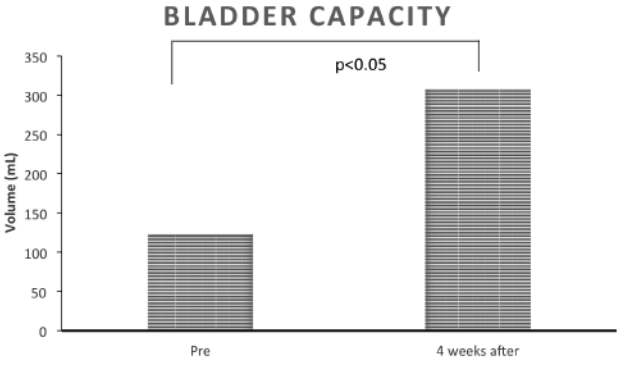

Figure 3. Bladder capacity of the patients before and after modified intravesical oxybutynin.

Table 1. Patients' classification according to the response evaluation.

	Group A	Group B	Group C
N/N%	26/ 54.16%	10/20.83%	12/25%
Symptoms	Disappearance of urgency and pain during urination	Disappearance of urgency and pain during urination	Continued feeling of urgency and pain during urination
Daytime urinations frequency (%)	70	50	10
Nocturnal urinations frequency (%)	100	50	20

Table 2. Patients' classification according to the response evaluation.

Patients	Mean of nocturnal urinations frequency before treatment	Mean of nocturnal urinations frequency after treatment	p
Female	4.58±1.78	1±0.33	0.028
Male	4.6±0.57	2.8±0.6	0.028

Table 3. Bladder capacity of the patients before and after modified intravesical oxybutynin.

	Pretreatment	4 weeks after	p
Bladder capacity (mL)	123.41±24.83	308.08±30.68	0.000

thought to be the presumed cause of the symptoms.[17] ∑These data corroborated the findings of Massad *et al*., who examined the effects of intrathecal and oral oxybutynin chloride and discovered that intrathecal instillation produced significantly greater plasma concentrations and was more effectively tolerated than oral administration. There were no discernible systemic negative effects, even at the noticeably higher levels.[20]

Furthermore, research conducted on lab animals has demonstrated that transvesic absorption of oxybutynin results in a reduced first-pass effect and, as a result, a favorable oxybutynin to desethyl-oxybutynin ratio. It is believed that this first-pass metabolite is the cause of the adverse anticholinergic effects.[21]

Additionally, after intravesical oxybutynin, there were statistically significant changes in bladder capacity in this trial. According to Madersbacher, intravesical oxybutynin resulted in a statistically significant rise in CC and decrease in maximal detrusor pressure in 13 individuals with full suprasacral spinal cord injuries.[22] O'Flynn and Thomas found that 12 out of 15 participants in their research saw a decrease in the frequency and amplitude of hyperactive contractions and incontinence episodes after receiving intravesical oxybutynin.[23] 9 of the 13 spinal cord injury patients receiving intravesical oxybutynin treatment showed improvements in bladder capacity and leak point pressure, according to Szollar and Lee.[24]

As this was a study using a small number of patients and a preliminary report, this data provides the possibility of another treatment option for OAB and/or detrusor hyperreflexia patients who do not respond to oral medication or who experience intolerable systemic side effects of anticholinergic drugs.

Conclusions

Multiple formulations of oxybutynin have been created with the goal of reducing side effects and improving tolerability. Over the past 3 decades, we have discovered that by changing the delivery method of this versatile compound, we can improve the therapeutic index and tolerability of the drug.

Intravesical delivery of oxybutynin has shown that the high rates of antimuscarinic side effects encountered with oral oxybutynin chloride can be avoided while maintaining therapeutic efficacy.

After analyzing the results of the treatment of 48 patients, we note that the instillation of OH into the bladder to treat hypertonic, idiopathic, refractory bladder that does not respond to oral treatment is a safe and effective method with good results and few complications. It is also acceptable for patients (especially females) who suffer from symptoms of intolerance or side effects of oral OH therapy, and it is necessary to present it in an appropriate pharmaceutical form that increases the positive clinical results.

References

1. Leron E, Weintraub AY, Mastrolia SA, Schwarzman P: Overactive bladder syndrome: evaluation and management. Curr Urol 2018;11:117-25.
2. Milsom I, Abrams P, Cardozo L, et al. How widespread are the symptoms of an overactive bladder and how are they managed? A population-based prevalence study. BJU Int 2001;87:760-6.
3. Haylen BT, de Ridder D, Freeman RM, et al. An International Urogynecological Association (IUGA)/International Continence Society (ICS) joint report on the terminology for female pelvic floor dysfunction. Int Urogynecol 2010;21:5-26.
4. Drake MJ: Do we need a new definition of the overactive bladder syndrome? ICI-RS 2013. Neurourol Urodyn 2014;33:622-4.
5. Song YS, Lee HY, Park JJ, Kim JH. Persistence and adherencenof anticholinergics and beta-3 agonist for the treatment of overactive bladder: systematic review and meta-analysis, and network meta-analysis. J. Urology 2021:205:1595-604.
6. Escobar CM, Falk KN, Mehta S, et al. Rethinking second-line therapy for overactive bladder to improve patient access to treatment options. Obstet Gynecol 2021:137:454-60.
7. Cakir SS, Degirmentepe RB, Atalay HA, et al. The effect of overactive bladder treatment with anticholinergics on female sexual function in women: a prospective observational study. Int Urol Nephrol 2019;51:27-32.
8. Yoshimura N, Chancellor MB. Current and future pharmacological treatment of overactive bladder. J Urol 2002;168:1897-913.
9. Noh JW, Lee B, Kim JH. Efficacy and safety of anticholinergics for children or adolescents with idiopathic overactive bladder: systematic review and meta-analysis. Int Urol Nephrol 2019;51:1459-71.
10. Jurgen P, Hans J, Uwe B, Theodor S. Combined intravesical and oral oxybutynin chloride in adult patients with spinal cord injury. Urology 2000;55:358-62.
11. Lehtoranta K, Tainio H, Lukkari-Lax E, et al. Pharmacokinetics, efficacy and safety of intravesical formulation of oxybutynin in patients with detrusor overactivity. Scand

J Urol Nephrol 2002;36:18-24.
12. Crane A, Isharwal S, Zhu H. Current therapeutic strategies in clinical urology. Mol Pharm 2018;15:3010-9.
13. Schroder A, Albrecht U, Schnitker J, et al. Efficacy, safety, and tolerability of intravesically administered 0.1% oxybutynin hydrochloride solution in adult patients with neurogenic bladder: a randomized, prospective, controlled multi-center trial. Neurourol Urodyn 2016;35:582-8.
14. Guerra LA, Moher D, Sampson M, et al. Intravesical oxybutynin for children with poorly compliant neurogenic bladder: a systematic review. J Urol 2008;180:1091-7.
15. Lazarus J. Intravesical oxybutynin in the pediatric neurogenic bladder. Nat Rev Urol 2009;6:671-4.
16. Mizunaga M, Miyata M, Kaneko S, et al. Intravesical instillation of oxybutynin hydrochloride therapy for patients with a neuropathic bladder. Paraplegia 1994;32:25-9.
17. Kennelly. MJ. A comparative review of oxybutynin chloride formulations: pharmacokinetics and therapeutic efficacy in overactive bladder. Rev Urol 2010;12:12-9.
18. Jacoby HI. Gastric emptying. In: Reference Module in Biomedical Sciences; 2017.
19. Kasabian NG, Vlachiotis JD, Lais A, et al. The use of intravesical oxybutynin chloride in patients with detrusor hypertonicity and detrusor hyper-reflexia. J Urol 1994;151:944-5.
20. Massad CA, Kogan BA, Trigo-Rocha FE. The pharmacokinetics of intravesical and oral oxybutynin chloride. J Urol 1992;148:595-7.
21. Buyse G, Waldeck K, Verpoorten C, et al. Intravesical oxybutynin for neurogenic bladder dysfunction: less systemic side effects due to reduced first pass metabolism. J Urol 1998;160:892-6.
22. Madersbacher, H. Control of detrusor hyperreflexia by intrav
esical instillation of oxybutynin hydrochloride. Paraplegia 1991:29:84-90.
23. O'Flynn KJ, Thomas DG. Intravesical instillation of oxybutynin hydrochloride for detrusor hyperreflexia. Br J Urol 1993;72:566-70.
24. Szollar SM, Lee SM. Intravesical oxybutynin for spinal cord injury patients. Spinal Cord 1996;34:284-7.