ORIGINAL ARTICLE

Overactive bladder and botulinum toxin type A management at the *Hospital General de México*

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ABSTRACT

Background: According to the 2002 definition by the International Continence Society, overactive bladder is a syndrome characterized by micturition urgency associated with frequency and nicturia, with or without urge incontinence. There are pharmacological treatments for this disease but refractory cases must be resolved by alternative means. The use of botulinum toxin type A in different doses (200 IU on average) has been reported in the international literature.

Methods: A descriptive study was carried out that included 15 female patients between 29-76 years of age who were diagnosed with drug-refractory overactive bladder. They were treated with 100 IU botulinum toxin type A applied to the detrusor muscle via cystoscopy. All patients had presented with moderate to severe clinical and urodynamic overactive bladder symptoms that importantly affected quality of life. They were evaluated before botulinum toxin application and 2-3 months after treatment by means of medical history, micturition diary, urodynamics (Total Bladder Capacity), assessment with overactive bladder and quality of life questionnaire (Potenziani-QOL-HV-26, 2005) and King's Health Questionnaire. Statistical analysis of variables was carried out using correlation tests and results were statistically significant.

RESUMEN

Antecedentes: De acuerdo con la *International Continence Society* (ICS) de 2002, la vejiga hiperactiva (VH) se define como un síndrome caracterizado por urgencia miccional asociada a frecuencia y nicturia con o sin incontinencia por urgencia. Existen tratamientos farmacológicos para este padecimiento sin embargo casos refractarios deben ser resueltos mediante otras alternativas. En la bibliografía mundial se ha reportado el uso de toxina botulínica tipo A, en diversas dosis (200 UI en promedio).

Métodos: Se realizó un estudio descriptivo, en el que se incluyó a 15 mujeres de entre 29 a 76 años, con diagnóstico de VH refractaria a tratamiento farmacológico y a los que se aplicó vía cistoscópica de 100 UI de toxina botulínica tipo A en el detrusor. Todas presentaban síntomas clínicos y urodinámicos de moderados a severos de VH con importante afectación en su calidad de vida. Todas fueron evaluadas previamente al tratamiento y a los dos o tres meses posteriores a la aplicación mediante historia clínica, diario miccional, urodinámica (Capacidad Vesical Total) y evaluación con los cuestionarios de vejiga hiperactiva y calidad de vida (Potenziani-QOL-HV-26,2005) y el cuestionario de salud *King´s*. El análisis estadístico: pruebas de correlación de las variables y fueron estadísticamente significativas.

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Results: All 15 patients presented with clinical and urodynamic improvement, but it was greater in those women under 50 years of age. There was a 66.6% improvement in patients in the overactive bladder and quality of life questionnaire, a 25.4% improvement in King's Health Questionnaire, 80.3% in First Micturition Desire and 92.6% in Total Bladder Capacity.

Conclusions: Medical management with botulinum toxin type A (100 IU) is an effective treatment for drug-refractory overactive bladder. There were no relevant adverse effects. However, the optimum dose of botulinum toxin type A that provides greatest efficiency and safety has yet to be established and so further studies need to be carried out.

Key words: Botulinum toxin, overactive bladder, Mexico.

Resultados: Las 15 pacientes presentaron mejoría clínica y urodinámica, siendo ésta mayor en las menores de 50 años. En el cuestionario de vejiga hiperactiva y calidad de vida hubo una mejoría de 66.6% en las pacientes; en el cuestionario de *King´s* de 25.4%, de 80.3% en el *Primer Deseo Miccional* y de 92.6% en la *Capacidad Vesical Total.*

Conclusiones: El manejo médico con toxina botulínica tipo A (100 UI), constituye un tratamiento efectivo para el manejo de VH refractaria a fármacos. No se presentaron reacciones secundarias relevantes. Sin embargo, todavía no se ha demostrado la dosis óptima de toxina botulínica tipo A que demuestre su mayor eficacia y seguridad, por lo que se considera necesaria la realización de estudios posteriores.

Palabras clave: Toxina botulínica, vejiga hiperactiva, México.

WINTRODUCTION

According to the 2002 definition by the International Continence Society (ICS), overactive bladder (OAB) is a syndrome indicative of lower urinary tract dysfunction characterized by urinary urgency associated with frequency and nicturia with or without urge incontinence. Wet OAB refers to overactive bladder with urge incontinence and dry OAB to overactive bladder without urge incontinence.[1,2] However in the 2003 revision, the ICS redefined their OAB definition based on symptoms (specifically urgency) rather than on urodynamic parameters and it was modified to include "any involuntary loss of urine".[3] OAB can be of neurogenic or idiopathic origin, the latter being the more frequent. In other words, the detrusor muscle is considered to be overactive when involuntary detrusor contractions are detected through urodynamic studies.[2]

Incontinence prevalence has been described in women to vary from 14- 40.5% (23.5% using the ICS definition). Urge incontinence and mixed incontinence represented a 51% average of these cases and 33% of OAB patients presented with urge incontinence. In the United States and Europe, average OAB prevalence is 35% in women above 18 years of age. This prevalence increases with age and is 27% at 45 years, 27% at 60 years, 34% at 75 years and 35% at 80 years of age.[2]

Etiology can be due to abnormalities of the lower urinary tract (infections, foreign bodies, tumors, etc.) or can be neurogenic (central nervous system, spinal medulla, peripheral nervous system), systemic (congestive heart failure, diabetes mellitus), iatrogenic, psychological, or due to poor dietary habits. Normal micturition includes the coordination of various structures such as the cerebral cortex, annular protuberance, the peripheral nervous system, the somatic nervous system, sensory afferent fibers, and lower urinary tract anatomical components. Likewise, central and peripheral neurotransmitters such as acetylcholine, dopamine, and nitric oxide, among others, play an important role.[2]

OAB syndrome is a frequent disease having a significant negative impact on quality of life. Intravesical botulinum toxin type A injection is being used with greater frequency as an intervention for drug-refractory OAB and there are a considerable number of case and series reports in the literature suggesting it has beneficial effects.[2-4,14,15]

The National Overactive Bladder Evaluation (NOBLE) study was carried out in the United States to provide a clinically valid research definition for OAB. The NOBLE study also calculated total OAB prevalence and individual disease burden and studied the differences among OAB groups (wet and dry). The survey included

5204 adults over 18 years of age. Dry OAB was defined as 4 or more episodes of urgency in the 4 previous weeks with a frequency of more than 8 times a day or resorting to one or more behavioral mechanisms (crossing the legs, walking, etc.) to control bladder hyperactivity. Wet OAB included the same criteria as dry OAB in addition to 3 or more episodes of urinary incontinence in the previous 4 weeks that clearly were not episodes of stress incontinence. Overall OAB prevalence was 16.9% in women and 16.2% in men and increased with age. Overall prevalence percentages of dry OAB and wet OAB in women were 7.6% and 9.3%, respectively.[1]

RISK FACTORS

In the same age group, women are twice as much at risk for urinary incontinence (UI) and OAB than men. Anatomical factors such as urethral length, prostate gland, size of pelvic floor musculature, and endopelvic fascia explain some of the differences in UI incidence between men and women, as well as in children.[5] Women tend to present with more stress and mixed UI, but the proportion of men and women presenting with urge incontinence is approximately the same.[6]

OAB risk factors are not sufficiently well known and the following, among others, have been indicated: neurological disease, infection, metabolic disease, stress, smoking, perimenopausal states, and sedentary lifestyle. Statistical evidence from different authors has indicated there is greater OAB prevalence in white, Hispanic and Asian women than in black women. Further studies are required to establish cultural influence in OAB incidence. There are common factors in both men and women such as neurological disease (Parkinson's disease, multiple sclerosis, spinal cord injury, and cerebrovascular stroke), diabetes, obesity, alcoholism, and smoking.[6]

ENTITIES ASSOCIATED WITH OAB

There are a series of clinical entities and diseases that frequently affect the genitourinary apparatus. It is fundamental that urologists, gynecologists, neurologists, and physicians be familiar with these conditions that overlap etiological factors and clinical manifestations of OAB. The objective is to have sufficient knowledge of the urological manifestations of the following conditions: urinary infection, menopause, genital prolapse and UI, gynecological neoplasia, urological neoplasia (bladder cancer), urinary lithiasis, lower urinary tract obstruction, neurological disorders, and diabetes mellitus.[6] At the same time it is necessary to maintain abreast of the new drugs available for treating OAB.[7]

ECONOMIC IMPACT

In 1995 in the United States, OAB represented a cost of 16.4 million dollars, divided among 12.4 million women and 4 million men. This is approximately 2% of the health budget for the United States population. The cost of OAB is greater than that of osteoporosis, gynecological cancer, and breast cancer, among others.[6]

CLINICAL DATA

Basic methods available at all health care service levels for the correct OAB diagnosis are medical history, physical examination, and micturition diary. A detailed and accurately performed anamnesis focuses not only on symptoms but also on possible risk factors, enabling the type of incontinence to be intuited and adequate complementary diagnostic tests to be ordered.

Another important datum that should be gotten from the medical history is the number of compresses or protectors used per day by the patient which serves to indirectly evaluate the severity of OAB with UI. Urinary characteristics can be evaluated starting with a micturition diary in which the patient writes down the number of micturition episodes and the length of their intervals, volume of urine voided, and incontinence events and their causes (stress or urgency) over a period of 3-7 days.

Physical examination should be carried out with the patient in the dorsal lithotomy position and with a full bladder. The evaluation of associated genital prolapse should include basic neurological exploration of the lumbosacral zone to determine pelvic floor muscle tone and bulbo-cavernous and anocutaneous reflexes.[1,2]

MORBIDITY

Table 1 shows the 12 principal reasons women presenting with OAB seek treatment.[1]

If OAB clinical manifestations are frequency, urgency, nicturia and urinary incontinence, the patient may also present with other alterations such as sexual dysfunction, depression, urinary infection, increased risk of falling and consequent risk of fracture, sleep loss, fear, and anxiety, among others. The patient is forced to modify his work and social activities, has to urinate more frequently, drink fewer liquids, carry out activities close to a bathroom or to know exactly where one is, wear dark clothing or use sanitary napkins or diapers.[3]

There was an association between depression and urge incontinence in a survey that used the Beck Depression Inventory. Its prevalence was 60% in patients

Table 1. Reasons why patients seek medical treatment.

Reasons for seeking treatment	*N* = 605	(%)
Worry that the condition might worsen	20	5
Necessity to begin to use sanitary napkins or diapers	4	3
Worry that the condition is not normal	12	4
Worry that leaks or urine loss are symptoms of a more serious disease	14	7
Interference with daily activities	6	6
Worry that odor resulting from leaks or involuntary urine loss might be apparent to others	8	8
Interference with physical activities	5	6
Increase in frequency of leaks or urine loss	3	5
Interference with work activities	0	8
Increase in the quantity of leaks or urine loss	2	3

Data from Coyne KS, et al. The impact of urinary urgency and frequency on health-related quality of life in overactive bladder: results from a national community survey. Value Health 2004; 7(4):455-63.

with idiopathic urge incontinence, 42% in patients with mixed incontinence and only 14% in patients with stress urinary incontinence. It is still not understood to what degree OAB alone contributes to sleep disorders because many persons, especially the elderly, complain of sleep disorders that are not related to an OAB nicturia component. Brown et al also observed, as previous studies had demonstrated, that when urge incontinence is associated with the OAB symptoms of frequency/urgency and nicturia, this combination can increase the risk of falls and fractures in elderly women by up to 26%.[2]

COMPLEMENTARY DIAGNOSTIC TESTS

URODYNAMIC STUDY

A fundamental aspect of OAB diagnosis in women is to identify those patients with OAB and UI and this precise diagnosis is only possible with a method that allows for objectively looking for involuntary detrusor contractions during the filling phase, and therefore urodynamic studies are essential for women seeking medical attention for UI/OAB.[7]

Urodynamics should confirm OAB and rule out detrusor hypoactivity. Bladder accomodation and emptying pattern should be evaluated. If the pattern is altered, differentiation must be made between bladder obstruction and hypocontractibility. An objective measurement of OAB intensity by means of leakage pressure points or maximum urethral closure pressure should be obtained, establishing, if that is the case, intrinsic sphincter deficiency. All of the above is decisive in choosing the appropriate treatment.[8-10]

OAB QUALITY OF LIFE QUESTIONS

Up to 67% of women with OAB complained that their symptoms affected their daily lives. Symptoms in 60% of women caused them sufficient discomfort to warrant medical consultation. Frequency and urgency together (59%) were almost as constant as urgency alone (66%) with respect to patient consultation motives. Presently the principal symptoms of OAB are considered to be urgency, frequency and nicturia. In fact, urgency has been observed to be importantly related to patient quality of life. Only 27% of patients seeking medical attention were taking medication for symptoms at the time they were studied. In one study Stewart et al evaluated disease impact by means of self-administered questionnaires about quality of life, depressed state, and sleep quality. After making adjustments due to concomitant disease differences and other demographic factors, women presenting with wet and dry OAB had significantly lower clinical quality of life subindices, more symptoms related to depression, and poorer sleep quality.[2]

Studies have recently been carried out to evaluate the effects of OAB on sexual function. A study using the Female Sexual Function Index (FSFI) evaluated sexual function in 21 premenopausal incontinent women. Mean FSFI scores for desire, excitation, lubrication, orgasm, satisfaction, and pain in the incontinent women were compared with 18 healthy continent women very close in age. Except for pain, scores were significantly lower in the incontinent women indicating that urinary incontinence significantly reduces sexual function in sexually active premenopausal women.[2]

HYGIENIC AND DIETARY MEASURES

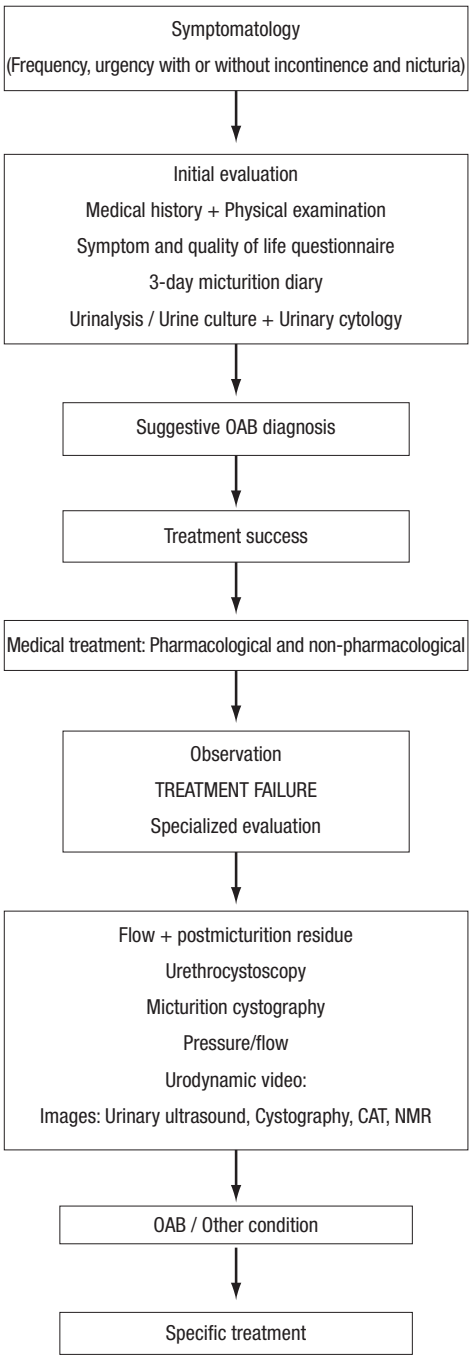
Acceptable treatment in overweight women is weight reduction. Currently, maintaining adequate weight is considered to be an effective preventive measure for pelvic floor overload. There is a demonstrable association between smoking and OAB, perhaps due to increase in abdominal pressure in the chronic smoker.[6,7]

Abundant water intake, especially before bedtime, is related with a greater number of UI episodes. Limiting this intake starting at the evening meal and reducing stimulating substances (alcohol, coffee, tea) can have beneficial effects on the number of leaks even though data is inconclusive. Measures for reducing constipation, changing the type of clothing (comfortable and loose-fitting) or modifying intake of drugs that affect continence can also be beneficial measures.[6,7,13-15]

PHARMACOLOGICAL TREATMENT

Even though the physiopathology of this syndrome is still not well understood, given that detrusor muscle contraction is measured principally by acetylcholine stimulation of muscarinic receptors, pharmacological management of this process is based on blocking the receptors with antagonist drugs. There are 5 different muscarinic receptor subtypes (M1-M5). Anticholinergic drugs act on M3 receptors and cause the bladder detrusor muscle to relax, together with increasing the urethral internal sphincter tone, which in turn increments total bladder capacity. In addition, antimuscarinic agents exert local inhibitory action on M2 receptors of the bladder afferent pathway, blocking bladder urgency symptoms during bladder filling phase and increasing urine volume.[4]

Immunoprecipitation receptor studies have identified the presence of M2 and M3 subtypes in smooth detrusor muscle. However, the ratio of number of M2 to M3 subtypes is 3:1. Despite the predominance of M2 receptors, data suggest that M3 receptors are more important in direct activation of smooth detrusor muscle contraction while M2 receptors appear to



Algorithm 1. Overactive bladder diagnostic algorithm

block smooth detrusor muscle relaxation by means of B-adrenergic receptor, and thus facilitate cholinergic contraction.[4,5]

It has been suggested that M3 muscarinic receptor selectivity is the mechanism by which antimuscarinic agents provide clinical effectiveness in OAB treatment while reducing the incidence of adverse effects and safety questions related to the blocking of other muscarinic receptor subtypes to a minimum. It has been suggested that avoiding M1 and M2 receptors would limit cognitive and cardiac adverse effects, respectively. However, unfortunately, M3 receptors are found in the intestine and salivary glands and also in the bladder, and therefore dry mouth and constipation that accompany M3 selectivity would not be reduced.[4,5]

All antimuscarinic agents cause secondary effects when administered at therapeutic doses. The most common are dry mouth, blurred vision and visual accomodation difficulty. Adverse effects tend to be more pronounced in elderly patients and these drugs are contraindicated in patients with narrow-angle glaucoma and lower urinary tract obstruction, since they can trigger urinary retention.[4]

TROSPIUM CHLORIDE

Trospium is an antimuscarinic agent that has been available in Europe for the last 20 years and its use has recently been authorized in the United States.[2] It is not yet available in Mexico.[3] It possesses three pharmacological properties that are different from those of other antimuscarinic drugs: 1) it is a derivative of a quaternary ammonium group with a positive charge and antispasmodic activity, 2) it is not metabolized by the P-450 (CYP450) cytochrome system in the liver, and 3) 60% of the trospium absorbed is excreted in urine without changing, like the pharmacologically active original compound.[2-5] The other currently available compounds are tertiary amines metabolized by the CYP450 system and excreted without changes or as active metabolites in small quantities. Dose indication is 20 mg every 12 hours.[4] Relative classification of available antimuscarinic agents for OAB treatment in relation to their lipophilia and potential ease for crossing the blood-brain barrier is calculated to be greater for darifenacin in comparison with oxybutynin and solifenacin and to be lesser for tolterodine and even less for trospium.[2] Trospium effectively improves key OAB symptoms, reduces urge incontinence episodes (21% of control), daily micturition episodes and increases urine volume emptied with each micturition four-fold.[2-5]. One study shows only 4% of patients treated presented with dry mouth.[2] Like quaternary amine, trospium does not easily cross the blood-brain barrier. This characteristic can be useful in elderly patients that are susceptible to central anticholinergic effects and that may be taking other anticholinergic drugs, thus increasing their total cholinergic charge. It has a strong affinity for M1-M5 subtypes and especially for M3.[2]

OXYBUTYNIN CHLORIDE

Oxybutynin chloride is a tertiary amine antimuscarinic agent that has anticholinergic, myorelaxant properties in smooth muscles and that acts as a local anesthetic (because of its similarity to amines such as lidocaine) and has a certain relative selectivity for M3 and M1 in regard to other subtypes.[2-5] It has an active metabolite, N-desethyl oxybutynin, that appears to be responsible for dry mouth (61%), due to its greater affinity for parotid receptors than for bladder receptors.[2] In addition, in the population over 65 years of age it can produce cognitive function deterioration since it crosses the blood-brain barrier and so its use in that population is not recommended.[4,5] Its effectiveness in reducing urinary frequency and incontinence is unquestionable in the medical literature. Urodynamically, it has been demonstrated to increase bladder capacity and it softens or annuls detrusor hyperactivity and delays initial micturition desire.[2] It can be used in children starting at 6 years of age. It comes in both fast-acting and slow-acting presentation forms at oral doses of 5, 10, and 15 mg and is equally effective at 20 mg/day or 5 mg every 8 hours.[2,4] It can also be administered by means of endovesical instillation, thus avoiding the systemic effects produced by its active metabolite. Saito et al published a study of 6 patients presenting with oral agent-refractory neurogenic OAB that were given modified intravesical presentation (oxybutynin chloride with hydroxypropyl cellulose). Cystometrography showed bladder capacity increase. A slow-acting intravesical system is being developed that is put in place and removed by means of cystoscopy and that releases oxybutynin for a period of one month.[4] Transdermal administration is as effective as oral administration and there are patches in presentations of 1.3, 2.6 and 3.9 mg that are applied every 3-4 days. They have a low incidence of adverse effects (such as dry mouth). However, there have been local reactions at the application site such as pruritus and erythema.[2] A Polish study evaluated transrectal administration with 5 mg of oxybutynin chloride every 12 hours in which 25% of patients reported improvement of OAB symptoms and only 13% complained of mild dry mouth.[2] Oxybutynin is the best anticholinergic agent for detrusor hyperactivity that has been studied since the 1960s. It has more market presentations and greater dosage flexibility than any other anticholinergic agent and continues to be the first-line reference treatment.[2]

TOLTERODINE

Tolterodine is a tertiary amine with relatively little lipophilia and crosses the blood-brain barrier less. It is a competitive antagonistic for the muscarinic receptor, and is not selective for any of the 5 muscarinic receptor subtypes (M1-M5) but has greater functional selectivity for the bladder than for the salivary glands and therefore has lower adverse effect incidence, with 19% dry mouth and 3% somnolence.[2-5] Initial passage of tolterodine through the hepatic metabolism is immediate and important, basically due to CYP 2D6- mediated oxidation and to CYP 3A4-mediated N-dealkylation. Its metabolite, 5-hydroxymethyl (5-HM) is the product of the predominant CYP 2D6 pathway and pharmacologically is equally as potent as tolterodine.[2] At a dose of 2 mg every 12 hours it reduces incontinence episodes by 60% and long-acting presentation of 4 mg/day reduces incontinence episodes by 71%, with a 21% and 24% urine volume average greater than the baseline, respectively.[3] Tolterodine was developed in response to the necessity for a more bladder-specific, well-tolerated antimuscarinic agent with fewer secondary effects.[2,4,5]

DARIFENACIN

Darifenacin is the first agent to have greater selective antagonist action on M3 muscarinic receptors. Its distinctive pharmacology gives this drug certain defined clinical characteristics in regard to possible secondary effects. Its clinical effectiveness in treating urinary urgency and incontinence has been demonstrated at doses of 7.5 and 15 mg/day, reducing episodes by 67% and 72%, respectively. The most frequent adverse effects are dry mouth (19-31%) and constipation (14%). Significant cognitive adverse effects have not been reported.[4,5]

SOLIFENACIN

Solifenacin is a tertiary amine antimuscarinic agent with a 4-fold greater affinity for M3 receptors than for salivary glands that inhibits carbachol-induced intracellular calcium mobilization.[2-5]. It is the only antimuscarinic agent that has been demonstrated to have a positive impact on nicturia.[3] At doses of 5 and 10 mg/day urgency episodes are reduced by 52%. It increases functional bladder capacity and reduces urgency, frequency and incontinence. In regard to adverse effects, 7-23% are related to dry mouth, 3% to constipation and less often to blurred vision. [2-5].

PROPIVERINE HYDROCHLORIDE

Propiverine hydrochloride is an antispasmodic agent by means of anticholinergic action and calcium antagonist effect that has demonstrated a 63% subjective improvement in patients receiving a 15 mg dose. A multicenter study compared its safety, tolerability, and effectiveness, together with oxybutynin, in children and adolescents. Results included an increase in bladder capacity and secondary effects of dry mouth and blurred vision in 9-17% of patients.[4,5]

LOCAL ADMINISTRATION OF OTHER DRUGS

Initial OAB treatment is with oral anticholinergic agents, but they often have adverse effects or lose their effectiveness over time and for these reasons patients abandon treatment. A viable therapeutic focus is down-regulation of sensitive nerves, treating them with neurotoxins (vanilloids) such as capsaicin or resiniferatoxin and cannabinoids. They act through the desensitizing of bladder type C afferent fibers. Resiniferatoxin is a capsaicin analog that is one thousand times stronger. There is a 53-83% clinical and urodynamic improvement in neurogenic bladder hyperactivity after its instillation into the bladder.[1] However, the hydrophobic nature of these neurotoxins makes it necessary to use ethanol as a cosolvent and saline solution as the instillation vehicle in the bladder. Ethanol produces inflammation in different tissues. Recent studies have demonstrated the superiority of non-alcoholic solvents for vanilloids over alcoholic solvents. Liposomes have also been used to try to overcome the water insolubility of vanilloids.[2]

B-3 ADRENOCEPTOR AGONIST PROMISE

There are beta adrenoceptors (B-AR) in the detrusor muscle whose function may be to mediate detrusor relaxation during urine storage. Three subtypes have been identified of which B3-AR agonists have been analyzed for their possible use in OAB treatment.[2] One study demonstrated that these agonists increase bladder capacity, reduce detrusor muscle excitability, temper bladder afferent activity and are a low risk for affecting bladder emptying.[6]

SACRAL NERVE STIMULATION (SNS) IN OAB

Various reflex mechanisms may be implicated in suppressing bladder overactivity by means of SNS. Afferent pathways that are projected into the sacral medulla may inhibit bladder reflexes through two mechanisms: 1) sacral interneuronal transmission inhibition and 2) direct inhibition of the bladder

preganglial neurons of the efferent branch of the micturition reflex circuit. This action prevents involuntary micturition (reflex) but does not necessarily suppress voluntary micturition. Studies report 50-70% effectiveness in relieving symptoms. When conservative OAB treatments fail, this minimally invasive technique offers a safe, reliable and long-lasting treatment of lower urinary tract dysfunction.[2]

BOTULINUM TOXIN TYPE A

First isolated by van Ermengem in 1897, botulinum toxin (BoNT) is the strongest known biological toxin. Three commercial BoNT preparations are available; two of them are type A neurotoxin (BTX-A) and the third is type B (BTX-B). Although they are produced by the same bacteria, Clostridium botulinum, their doses and potencies are different and therefore not interchangeable. In 1999, Stohrer et al first described BTX-A use in treating OAB. Since then various articles and expert-reviewed summaries have been available to the scientific community.[2,8,9,15-21]

BOTULINUM TOXIN ACTION MECHANISM

BoNT produces temporal chemodenervation in motor nerve endings through the following steps: 1) the toxin bonds to cholinergic nerve ending acceptors, 2) the molecule is internalized in the cytoplasm of nerve endings in its own vesicle, 3) when it is inside the nerve, BoNT interferes with cholinergic vesicle exocytosis, producing chemodenervation and nerve contraction reduction, 4) BoNT-specific cleavage-activating proteins (SNAP-25 for BTX-A and VAMP for BTX-B) are responsible for acetylcholine coupling and fusion of the acetylcholine vesicle with the presynaptic membrane which in turn interferes with neurotransmitter release, producing muscle relaxation, 5) terminal gemmation is produced over time; these buds land and form low-level transitory neuromuscular unions that release acetylcholine, 6) and finally the original terminal functional plaque is reestablished and the buds return; at this point some patients have a return of symptoms.[2,10]

The combination of temporal gemmation and reactivation (the possibility of releasing acetylcholine and perhaps other neuromessengers) of the original nerve ending is responsible for the completion of therapeutic activity.[2, 11, 22-25]

EFFERENT CHOLINERGIC EFFECT

The clinical success of BoNT intradetrusor injections is upheld by basic science research that demonstrates the effectiveness of BoNT on autonomous nerves. Smith et al found important reductions of acetylcholine release marked in normal rat bladders that had been injected with BTX-A after high but not low stimulation frequency. Somogyi et al showed that muscarinic presynaptic facilitating mechanisms are regulated at high frequency in cholinergic nerve endings in bladders in rats with spinal cord injury, provoking a greater contractile response relative to lower stimulation frequency. If there are similar relations in human bladders, BTX-A may be effective in treating uninhibited, non-voiding contractions, characteristics of all forms of detrusor hyperactivity.[2, 17, 24-26]

AFFERENT CHOLINERGIC EFFECT

BoNT effectiveness under conditions of detrusor hyperactivity may be due to an inhibiting effect on the detrusor muscle. Certain effects of the drug may also be mediated by afferent (sensitive) entrance alteration. In addition to receiving cholinergic innervation it has also been demonstrated that human urothelium releases resting acetylcholine. And so, acetylcholine, released by the urothelium and acting on nearby muscarinic (urothelium or afferent nerve) receptor populations or neuronal acetylcholine sources that bond to urothelial or afferent nerve muscarinic receptors, could have an important impact on the sensitive bladder entrance to the central nervous system and BoNT treatment can act on that.[2,12]

DIAGNOSTIC VALIDATION INVENTORIES

In an effort to be able to apply Spanish language diagnostic inventories adapted to Mexico, the following instrument for diagnosing overactive bladder is proposed. It is intended to be validated in the near future. These diagnostic self-evaluation instruments help the patient become aware of his or her condition (by providing information that will be of diagnostic use) and they take very little time to fill out. In addition, answers given by the patient are basic for a complete evaluation of the impact of symptom distress and quality of life, as well as for OAB treatment.[5,6,27]

KING'S HEALTH QUESTIONNAIRE

King's Health Questionnaire was developed by Kelleher and Cardozo in King´s College hospital, in Great Britain. It evaluates the impact of urinary incontinence on quality of life and also incorporates the objective evaluation of certain urinary symptoms. It evaluates 10 domains related to quality of life and urinary symptoms

offering reliability and validity that is appropriate for both men and women. It is useful for evaluating quality of life in incontinent women with overactive bladder receiving attention in different types of health care facilities and for evaluating the results of different applied treatments since all aspects of the questionnaire are sensitive to changes after treatment.[28] Urinary incontinence is evaluated as follows: a score of 0-30 is mild UI, 33- 47 moderate UI, 47-64 severe UI, and a score above 47 indicates severe quality of life alteration (**Table 2**).

OAB is not a vital risk process as such, but it significantly deteriorates patient quality of life, limiting self-sufficiency and reducing self-esteem and even leading to depression.

The impact of OAB on quality of life related to health can be greater than that caused by certain chronic illnesses such as diabetes mellitus or high blood pressure, among others.

In regard to patients with OAB diagnosis, the authors' hospital department does not have specific methods that evaluate quality of life impact in the patient evaluation process- an extremely important parameter for deciding which patients are candidates for conservative or non-conservative (surgical) treatment and its correlation with urodynamic and clinical diagnosis. Therefore the authors decided to carry out the present study in order to integrate into their daily practice questionnaires for evaluating quality of life impact before and after surgical treatment with the technique of botulinum toxin type A application in drug-refractory overactive bladder management carried out in the their department at the neurourology and pelvic floor dysfunction clinic. The study attempts to show that the selection of patients with this diagnosis that undergo the abovementioned surgical technique is adequate and in addition to identify the impact on quality of life parameters related to health (King's Health and Overactive Bladder questionnaires).

The present study is justified by offering an improved medical attention model to all patients seen in the authors' service through the incorporation of questionnaires in daily practice that evaluate quality of life, state of health, and urinary incontinence on a par with health institutions in developed countries. The selection of patients requiring this type of clinical management will also be improved. The authors believe the introduction of specific tests in carrying out OAB diagnosis in patients suspected of having that pathology will allow for better selection of patients needing surgical procedure due to pharmacological failure for the purpose of reestablishing their quality of life and urodynamic parameters.

"We believe botulinum toxin type A application in drug-refractory overactive bladder will significantly improve patient quality of life and urodynamic parameters."

Table 2. Overactive bladder and quality of life questionnaire (POTENZIANI-QOL-HV-26, 2005).

FINAL SCORE	
Mild impact (minimum) on quality of life	(QOL) = 0 a 10 points
Moderate impact on quality of life	(QOL) = 11 a 26 points
Severe impact on quality of life	(QOL) = 27 a 52 points

In contrast to other studies found in the literature that manage 200 IU, the present study used 100 IU with the goal of being able to obtain similar results.

The principal objective of the present study was to evaluate the effectiveness of botulinum toxin type A application in patients with drug-refractory overactive bladder by means of quality of life and urodynamic parameters. Other objectives were:

- to identify the benefits of botulinum toxin type A management, validated by quality of life and overactive bladder questionnaires
- to compare botulinum toxin type A management benefits by means of the principally affected urodynamic parameters in OAB (first micturition desire and bladder capacity)
- to improve clinical and therapeutic decisions by evaluating the impact on health of the patient diagnosed with OAB
- to incorporate questionnaires in daily practice in the authors' department that quickly, effectively and reliably evaluate the impact on quality of life of such severe pathologies as OAB
- to offer improved quality in medical attention that are on a par with international standards
- to contribute to research by broadening the field of knowledge through incorporating patient feelings by means of strategies and methods from other disciplines such as psychometrics and the design and construction of questionnaires and inventories.

METHODS

An analytical cross-sectional study was carried out at the Urology Service of the *Hospital General de México* over a period of 6 months. King's Health Questionnaire and Potenziani Quality of Life and Overactive Bladder

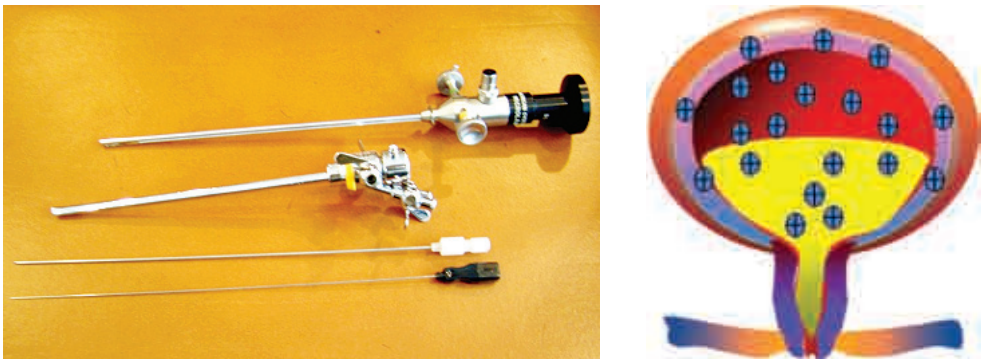


Image 1. Application by means of 23-gauge/8mm 5 F 35 cm long flexible needle of 100 IU divided among 30 sites covering the entire detrusor muscle surface.

Table 3. Potenziani overactive bladder and quality of life questionnaire.

Patient	Potenziani OAB questionnaire before toxin	Potenziani OAB questionnaire after toxin
1. 76th	35	23
2. 55th	48	15
3. 46th	45	18
4. 44th	50	17
5. 38th	51	13
6. 60th	38	21
7. 40th	48	16
8. 29th	50	19
9. 32nd	45	17
10. 37th	48	14
11. 62nd	36	22
12. 35th	44	11
13. 42nd	39	13
14. 39th	47	17
15. 43rd	40	16

Descriptive statistics 3			
		OABQ before treatment	OABQ after treatment
N	Valid	15	15
	Missing	0	0
Mean		44.2667	16.8000
Median		45.0000	17.0000
Mode		48.00	17.00
Standard deviation		5.35146	3.42679
Variance		28.638	11.743
Range		16.00	12.00
Minimum		35.00	11.00
Maximum		51.00	23.00

Correlations 3			
		OABQ before toxin	OABQ after toxin
OABQ before toxin	Pearson correlation	1	-.515*
	Significance (bilateral)		.050
	N	15	15
OABQ after toxin	Pearson correlation	-.515*	1
	Significance (bilateral)	.050	
	N	15	15

*Correlation is significant at 0.05 (bilateral).

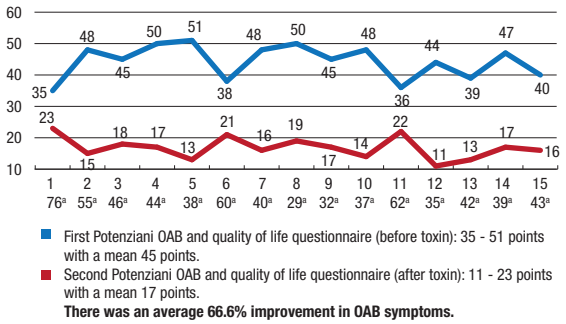


Image 2. Potenziani overactive bladder and quality of life questionnaire score.

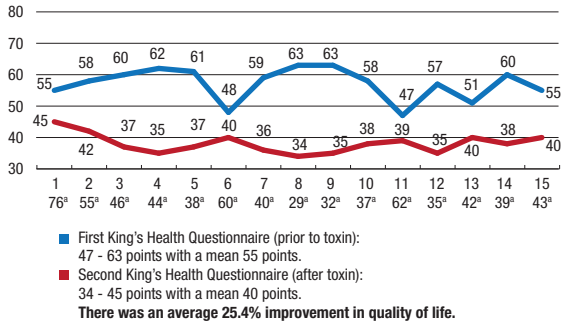


Image 3. King's Health Questionnaire score.

Questionnaire were applied to evaluate patient quality of life in relation to overactive bladder (OAB). Urodynamic parameters were obtained pre-application and post-application of 100 IU of botulinum toxin type A (BTX-A).

Population and sample size: A total of 15 women patients ranging from 29-76 years of age presenting with drug-refractory OAB were treated with cystoscopic injection of BTX-A into the detrusor muscle. Two patients presented with neurogenic OAB (Parkinson's disease). All patients presented with moderate to severe clinical and urodynamic OAB symptoms with an important impact on quality of life and had not responded to conservative or drug treatments and therefore were offered this alternative. Refractoriness was defined as inadequate control of symptoms after 2 or more drug therapy attempts and 1 or more OAB first-line treatments. All patients gave their informed consent after BTX-A administration technique and possible side effects were explained, especially the possibility of requiring intermittent catheterization or of receiving a second application at 6 months if symptoms returned.

The authors' hospital medical supply room provided the BTX-A doses of 100 IU. In the operating room the 100 IU were diluted in 8 mL of saline solution at 9%. Then 4 of those 8 mL were taken with a 20 cc syringe and diluted in another 11 mL of saline solution, for a total of 15 mL. This was repeated with the other 4 mL with a second syringe for a sum total of 2 syringes and 30 mL, each mL containing 3.3 BTX-A units. By means of cystoscope the bladder was filled with 100 mL of saline solution and the 100 IU were applied at 30 sites covering the entire detrusor muscle surface with a 23-gauge/8mm 5 F 35 cm long flexible needle. The 1 cm space surrounding the ureteral openings was not inoculated. Patients were released the following day (**Image 1**).

All patients were evaluated prior to treatment and at 2-3 months after BTX-A application by means of medical history, micturition diary, urodynamics, and evaluations with OAB and quality of life questionnaire (Potenziani QOL-HV-26, 2005) and King's Health Questionnaire.

Inclusion criteria:

1. Women patients over 18 years of age diagnosed with neurogenic or idiopathic OAB by means of clinical and urodynamic parameters.
2. Patients with or without stress incontinence in addition to OAB.
3. Patients who agreed to fill out the proposed questionnaires.

Exclusion criteria:

1. Patients having undergone prior pelvic floor surgery.
2. Patients diagnosed with urinary incontinence and cystocele.
3. Patients having undergone other bladder instillation techniques.
4. Patients with a history of neuromodulation.
5. Patients requiring a different surgical procedure for their particular pathology.

Statistical analysis: Statistical analysis was carried out using the Windows Statistical Package for the Social Sciences (SPSS) version 16 program. Descriptive analyses were carried out by means of percentages and means. The inferential tests used were Pearson correlation coefficient and Wilcoxon test for study variables. There was statistical significance when $P < 0.05$.

RESULTS

The study included a total of 15 patients from 29-76 years of age with a mean age 45.2 years. All 15 patients

Table 4. King´s Health Questionnaire.

Patient	King´s questionnaire before toxin	King´s questionnaire after toxin
1. 76th	55	45
2. 55th	58	42
3. 46th	60	37
4. 44th	62	35
5. 38th	61	37
6. 60th	48	40
7. 40th	59	36
8. 29th	63	34
9. 32nd	63	35
10. 37th	58	38
11. 62nd	47	39
12. 35th	57	35
13. 42nd	51	40
14. 39th	60	38
15. 43rd	55	40

Statistics 4			
		King's before toxin	King's after toxin
N	Valid	15	15
	Missing	0	0
Mean		57.1333	38.0667
Median		58.0000	38.0000
Mode		55.00a	35.00a
Range		16.00	11.00
Minimum		47.00	34.00
Maximum		63.00	45.00

Correlations 4			
		King's before toxin	King's after toxin
King before toxin	Pearson correlation	1	-.570*
	Significance (bilateral)		.027
	N	15	15
King after toxin	Pearson correlation	-.570*	1
	Significance (bilateral)	.027	
	N	15	15

*Correlation is significant at 0.05 (bilateral).

presented with clinical and urodynamic improvement after treatment. Improvement was greater in patients under 50 years of age.

Clinical effectiveness was evaluated with the Potenziani overactive bladder (OAB) and quality of life questionnaire (**Table 3, Statistics 3, and Correlations 3**) in which there were changes in the scores of various domains and principally in reduction of or zero use of protectors as well as in the domains of nicturia and urinary urgency (**Image 2**).

As a consequence of clinical improvement, all patients presented with quality of life improvement (**Table 4, Statistics 4, and Correlations 4**), reflected in the King's Health Questionnaire scores, and there was improvement in all domains (**Image 3**). In relation to urodynamic evaluation

(**Table 5, Statistics 5**) two important parameters that are affected by this entity - first desire micturition volume and maximum bladder capacity - were assessed (**Image 4**). Urine capacity for presenting first micturition desire improved in all patients, principally those under 50 years of age.

Table 6 (**Statistics 6 and Correlations 6**) shows that all patients presented with important improvement with respect to total bladder capacity (**Image 5**). Patients 1 and 11 were the Parkinson's disease patients and they presented with significant improvement.

DISCUSSION

OAB is a highly prevalent pathology in developed countries. In Mexico there are a variety of quality of life questionnaires available but they are not applied as standard practice by all clinicians. When such questionnaires are not used, the evaluation of treatment response becomes subjective. Many patients present with severe symptoms that improve only slightly with anticholinergic drugs or they do not tolerate them for different reasons and so alternative treatments are required.[4,21]

Pelvic floor electro-stimulation, when carried out at low frequency, relaxes the detrusor muscle (by causing sensitive afference with inhibitory efference through the hypogastric nerve) which in some cases improves OAB. Presently electro-stimulation and biofeedback are used to reinforce pelvic floor exercises in patients with mild to moderate stress incontinence.[1,7] Widely used intravesical drugs are the vanilloids: capsaicin and resiniferatoxin. They act by desensitizing type C afferent bladder fibers.[1,2,6] Botulinum toxin type A was initially used in neurogenic bladder patients: injecting the toxin in the external sphincter in cases of vesicosphincter dyssynergy and injecting it in the detrusor wall in cases of neurogenic OAB. [7,12]

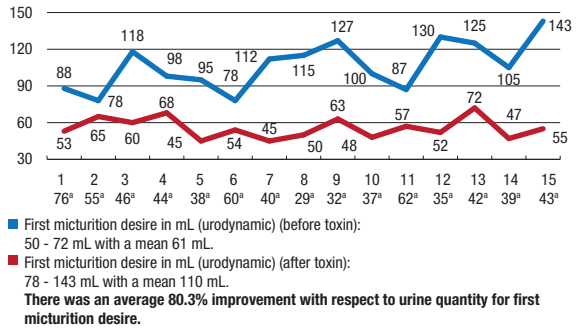


Image 4. Capacity in mL at first micturition desire (urodynamics).

Over the last few years, articles on neurogenic and non-neurogenic OAB have been published that show its effectiveness.[10,15,19,22,24-26] The toxin's most well-known action mechanism is the inhibition of acetylcholine release at the neuromuscular junction level resulting in transitory paralysis of the musculature.[1,3,7,8,12] In the majority of medical centers the solution is prepared by diluting 100 IU of toxin in 10 mL and administering a total of 200 IU in the detrusor by injecting 1 mL, in other words 10 IU, of toxIn the present study each inoculated mL was equivalent to 3.3 IU of toxin. Its effect was apparent 24-48 hours after application and lasted from 3-9 months, although in the majority of studies duration has been 9 months.[1]

The majority of patients in the present study reported the onset of effects at 48 hours after toxin administration. All patients experienced clinical response and the greatest benefits were seen in patients under 50 years of age. Clinical improvement lasted 3 months in all patients. BTX-A treatment is a well-tolerated procedure and no important side effects have been reported to date. Mild hematuria, pelvic pain and self-limiting dysuria may present. As has been reported in other publications, there was clinical improvement after toxin administration that was reflected in Potenziani OAB and quality of life questionnaires and in changes in urodynamic studies (volume increase at first micturition desire and increase in bladder capacity).

CONCLUSIONS

After having carried out statistical analysis with the Windows SPSS version 16 program in which variables were correlated using the Pearson coefficient and their relation was evaluated with a *P* of 0.05, and having made comparative graphs of scores before and after treatment in each of the categories, the authors concluded that

Table 5. Bladder capacity comparison at first micturition desire.

Patient	1st MD before toxin (mL)	1st MD after toxin (mL)
1 76th	53	88
2 55th	65	78
3 46th	60	118
4 44th	68	98
5 38th	45	95
6 60th	54	78
7 40th	45	112
8 29th	50	115
9 32nd	63	127
10 37th	48	100
11 62nd	57	87
12 35th	52	130
13 42nd	72	125
14 39th	47	105
15 43rd	55	143

Statistics 5			
		MD before toxin	MD after toxin
N	Valid	15	15
	Missing	0	0
Mean		55.6000	106.6000
Median		54.0000	105.0000
Mode		45.00	78.00
Range		27.00	65.00
Minimum		45.00	78.00
Maximum		72.00	143.00

BTX-A treatment was effective in all patients with drug-refractory OAB and that its intravesical application is a promising treatment despite the fact that enough data is not yet available from controlled studies on its benefits and safety in comparison with other interventions.

No relevant side effects were encountered. Patients under 50 years of age were observed to present with greater symptom improvement that was reflected in important questionnaire score reduction as well as in urodynamic studies in which there was an increase in total bladder capacity and first micturition desire urine quantity. This was not true in patients above 50

Table 6. Total bladder capacity comparison.

Patient	TBC before toxin (mL)	TBC after toxin (mL)
1 76th	95	135
2 55th	91	160
3 46th	128	210
4 44th	180	275
5 38th	115	220
6 60th	105	205
7 40th	144	290
8 29th	108	232
9 32nd	80	205
10 37th	88	215
11 62nd	139	188
12 35th	120	335
13 42nd	140	310
14 39th	130	288
15 43rd	175	262

Statistics 6			
		BC before toxin	BC after toxin
N	Valid	15	15
	Missing	0	0
Mean		122.5333	235.3333
Median		120.0000	220.0000
Mode		80.00a	205.00
Range		100.00	200.00
Minimum		80.00	135.00
Maximum		180.00	335.00

Correlations 6			
		BC before toxin	BC after toxin
BC before toxin	Pearson correlation	1	.558*
	Significance (bilateral)		.030
	N	15	15
BC after toxin	Pearson correlation	.558*	1
	Significance. (bilateral)	.030	
	N	15	15

*Correlation is significant at 0.05 (bilateral).

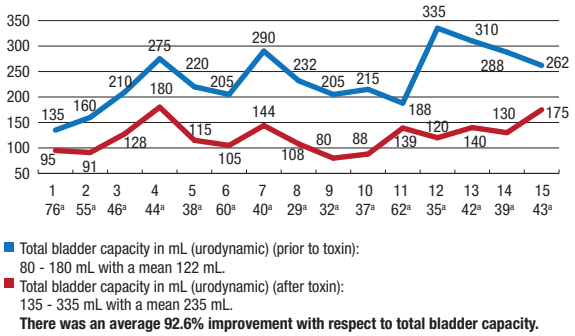


Image 5. Total bladder capacity in mL (urodynamics).

years of age in whom there was less improvement in clinical symptom score reduction and urodynamic parameters. The majority of published studies manage doses of 200-300 IU BTX-A toxin applied to the detrusor muscle. In the present study important benefits were observed with 100 IU. In addition, improvement in the majority of patients lasted for 5 months after BTX-A application. However optimum BTX-A dose in relation to effectiveness and safety has yet to be demonstrated and it is important to keep in mind that BTX-A application in the lower urinary tract has not yet been approved by all regulatory agencies.

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