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Research Article

Assessing Effectiveness of 'Onabotulinumtoxin A' (Botox®) Intradetrusor Injection for Overactive Bladder Patients after Endoscopic Interventions for Benign Prostatic Hyperplasia

Saitta G,* Di Paola G, Mantovani FA, Meazza A, Seveso M

ICCS - Istituto Clinico Città Studi, via Niccolo' Jommelli 17, Milan, Italy

Abstract

Introduction: Urge urinary incontinence (UUI) is a chronic debilitant condition that characterize some overactive bladder (OAB) patients in absence of any urinary tract infection (UTI). In our center we use intradetrusor injection of 'Onabotulinum toxin A' as second step after medical therapy failure in men who have underwent also to endoscopic surgery for BPH. The objective of this study is to verify the improvement in the patients' quality of life (QoL) and also to evaluate the effective dose over time.

Materials and Methods: We observed 40 male patients between January 2019 and January 2021, previously treated with oral drugs (anti-muscarinic and/or beta-3 adrenergic) and with surgical endoscopic approach (TURP, HoLEP, ThuLEP), 10 of these had pathologies - 4 of them neurological. These last patients were injected by 200U, all the others (36) by 100U - Botox®; Allergan, Irvine, CA, USA. Follow-up included monitoring of the following parameters at 3,6,12,24 months: urinary leaks (PAD test), Clean Intermittent Catheterization (CIC), OAB questionnaires, side effects. All patients underwent urodynamic examination before and 6 months after injection.

Results: The mean age was 60 years. 2 patients (5%) had early adverse effects after injection (1 vomiting, 1 pelvic pain), 4 (10%) needed CIC at 3 months, 1 of them also at 6 months (he was among the 4 neurological patients who underwent 200U dose). 38 (95%) answered positively to the questionnaire. Botox® treatment showed a reduction in urinary leakage at 3 and 6 months compared to medical therapy and a significant lowering of Pdet at 6 months ($p<0.05$). Both 100U and 200U doses proved to be effective up to one year after endoscopic treatment ($p<0.05$). The side effects at 3 months were 1 haematuria and 3UTI - 1 also recurred at 6 and 12 months

Conclusions: Botox® is a valid therapeutic option for OAB patients. 100U appears as an effective dose, however after 12 months it seems to lose its effect. There were no clinical relevant differences between 100 and 200U doses. Intradetrusor injection of 'onabotulinum toxin A' can be applied also in men affected by BPH who have previously undergone endoscopic prostatic surgery.

Keywords: Urge urinary incontinence, Over active bladder, Botox®, Intradetrusor injection, Benign prostatic hyperplasia

Abbreviations: 5-ARI: 5-Alpha Reductase Inhibitor; AUA: American Urological Association; BPH: Benign Prostatic Hyperplasia; CIC: Clean Intermittent Catheterization; EAU: European Association of Urology; ICS: International Continence Society; IIQ-7: Incontinence Impact Questionnaire; IPSS: International Prostate Symptom Score; IUSS: Indevus Urgency Severity Scale; KHQ: King' Health Question-

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*Corresponding author: Giuseppe Saitta, ICCS - Istituto Clinico Città Studi, 20131 Milan, Italy

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naire; LUTS: Lower Urinary Tract Symptoms; OAB: Over Active Bladder (i-: idiopathic; n-: neurogenic; -q: questionnaires); OABSS: Overactive Bladder Symptoms Score; PPBC: Patient Perception of Bladder Condition questionnaire; PSA: Prostate-Specific Antigen; PVR: Post-Void Residual urine; Qmax: maximum peak flow; QoL: Quality of Life; SNM: Sacral Neuro Modulation; SUI: Stress Urinary Incontinence; UDI-6: Urogenital Distress Inventory; UTI: Urinary Tract Infection; UUI: Urge Urinary Incontinence

Introduction

Urge Urinary Incontinence (UUI) is an annoying condition in which patients have to empty some urine volumes suddenly and with urgency.[1]

Over Active Bladder (OAB) is defined by International Continence Society (ICS) as urgency with or without UUI but usually with urinary frequency and nocturia in the absence of any Urinary Tract Infection (UTI).[2] OAB can be divided into two groups: idiopathic (iOAB) or neurogenic (nOAB) if there is an underlying neurological disease, such Parkinson's disease, ecc.[3]

There are many different data about the prevalence of OAB and the distribution between women and men, but most of the studies agree on the fact that it impacts public health especially in the elderly population, which is constantly increasing.[4]

Bladder capacity can be determined by '1-2-3 days' diary, uroflowmetry with ultrasound control of Post-Void Residual (PVR) volume, cystometry,[5] cystoscopy, but OAB is usually diagnosed after performing a complete urodynamic examination; some questionnaires can help to assess better this condition and can represent tools for treatment[6]: e.g. Overactive Bladder Symptoms Score (OABSS),[7] Indevus Urgency Severity Scale (IUSS),[8-9] International Prostate Symptom Score (IPSS),[10] Urogenital Distress Inventory (UDI-6), Incontinence Impact Questionnaire (IIQ-7),[11] King' Health Questionnaire (KHQ),[12] Patient Perception of Bladder Condition questionnaire (PPBC).[13]

A conservative management is considered the first-line treatment, with the aim of reducing urinary frequency and increasing bladder volume. These therapies include lifestyle interventions such as fluid management, control of voiding time, urge suppression techniques, pelvic floor muscle physiotherapy to interrupt detrusor contractions. Second-line treatment includes oral pharmacotherapy: anti-muscarinic or β3-adrenoreceptor agonist.[14] Several antimuscarinic drugs have been studied: oxybutynin, tolterodine, solifenacin, darifenacin, trospium, fesoterodine, propiverine, imipramine.[15-20] Oxybutynin is a lipophilic tertiary amine that is activated by first-pass metabolism and has direct muscle relaxant effect, local anaesthetic and antimuscarinic properties with high affinity for muscarinic receptors in the bladder.[21] It can be added on treatment patients refractory to one other antimuscarinic drug.[22]

Tolterodine's active liver metabolite presents similar selectivity for bladder muscarinic receptors.[23-24] Several trials have demonstrated a significant reduction in frequency and incontinent episodes, safety and efficacy were also compared to placebo and oxybutynin;[25-30]mthis treatment can increase bladder capacity.[31-32]

Solifenacin(Incoves®) demonstrated its efficacy on reducing urgency and PVR and on improving maximum peak flow (Qmax), although less potent than oxybutynin and tolterodine.[33-36] Darifenacin is an effective tertiary amine, presenting moderate adverse events.[37-38] Trospium chloride is a quaternary ammonium compound non-selective for muscarinic receptors, but some trials have demonstrated improvements in maximum cystometric capacity in comparison to placebo and similar oxybutynin effect in increasing bladder capacity and reducing maximum voiding detrusor pressure.[39-42]

Fesoterodine was considered the best anticholinergic by a 2021 multicriteria decision analysis model and better than the β3 adrenoceptor agonist mirabegron and solife- nacin/mirabegron drug combinations.[43] Propiverine has shown to increase bladder capacity and compliance, combining anticholinergic and calcium channel blocking actions.[44-46] Imipramine and other tricyclic antidepressants can be used for their anticholinergic activities and capacity to decrease bladder contractility.[47-49]

The most common side effects of antimuscarinic drugs are dry mouth, constipation, blurred vision.[50] Mirabegron was the first β3-adrenoreceptor agonist approved for OAB treatment, showing similar efficacy to antimuscarinic drugs and fewer adverse effects.[51-55] Association therapy with antimuscarinic plus β3-adrenoreceptor agonist can be considered after monotherapy for improving efficacy with low rates of side effects. Sacral neuromodulation (SNM), posterior tibial nerve stimulation (PTNS), augmentation cystoplasty and some other emerging therapies could be considered.[57] Onabotulinum toxin A intradetrusor injection is an effective treatment in patients refractory to antimuscarinics.[58]

Botulinum toxin is a potent neurotoxin produced by *Clostridium botulinum*, Gram-negative anaerobic bacteria, that inhibits calcium-mediated release of acetylcholine vesicles at the presynaptic neuromuscular junction acting on peripheral cholinergic nerve endings.[59] Seven serologic forms of botulinum toxin exist, but serotype A is the most commonly used for medical applications.[60] Every toxin presents a heavy and light chain linked by a disulfide bond.[61,62] The heavy chain determines connection specificity, while the light chain consists of the intracellular toxic portion.[63-64] After internalitazion of the heavy and light chains in the neuronal cell, a disulfide

reaction separates the chains and the light ones bind to the acetylcholine vesicles, acting as a zinc-dependent endopeptidase to cleave peptide bonds and prevent acetylcholine vesicle fusion with the plasma membrane, so inhibiting acetylcholine exocytosis and neurotransmission at the presynaptic junction that results in a flaccid paralysis of the muscle.[65-67]

Many articles have described and reviewed its use, indications, dose, administration, success rates and limitations. In our center we use intradetrusor injection of 'Onabotulinum toxin A' as second step after medical therapy failure in men who have underwent also to endoscopic surgery for Benign Prostatic Hyperplasia (BPH).

The aim of this study was to verify the improvement in the patients' quality of life (QoL) and also to evaluate the effective dose over time, in order to plan future treatments carefully.

Materials and Methods

Patient selection

This study included 40 consecutive male patients between January 2019 and January 2021, all with urodynamic diagnosis of OAB and previously treated with oral drugs (anti-muscarinic and/or β3 adrenergic).

10 of these patients (25%) presented some other phatologies, 4 of them have neurological diseases resulting as nOAB (10%), the other ones were iOAB patients (90%).

These 40 men had also irritative and obstructive Lower Urinary Tract Symptoms (LUTS) non-responsive to alpha-litic drugs (alfuzosin, silodosin, tamsulosin) and to 5-ARI (dutasteride, finasteride), so they underwent to endoscopic disobstructive interventions before toxin injection, sometimes also in other centers (28 ThuLEPs, 8 TURPs, 4 HoLEPs).

Parameters Measured

The following aspects were considered pre- and post-procedure at 3,6,12,24 months, in order to assess the efficiency of the technique: if there were any urinary leaks, the measure of the eventual leakage by considering the PAD test, if Clean Intermittent Catheterization (CIC) was necessary, Quality of Life (QoL) was assessed by OAB questionnaires, all complications were registered.

Description of the Technique

Equipment

1) Onabotulinum toxin A (100U)
2) Rigid cystoscope (telescope 70º/0º, bridge, and sheath)
3) Needle 22-27 Gauge and 4mm (70cm)
4) Two Syringes 10ml
5) Two Lidocaine 2% 10ml
6) Sodium Bicarbonate (8.4%) Injection (10ml)
7) Lidocaine gel
8) Foley 16Ch
9) Two Saline solutions 10ml
10) One Saline solution 50ml

Doses

The most common doses utilised were 100 UI for iOAB and 200UI for nOAB.

Surgical technique

The patient is placed in the lithotomy position. A gentle OTIS urethrotomy is performed if necessary. Rigid cystoscope is positioned and a 22G needle is inserted into the bladder wall and withdrawn halfway prior to injection.[68] After local anaesthesia, a fine sheath (27G) is introduced through the working channel of the cystoscope and the fine needle is passed through the sheath.[69-70] 20 injections are performed throughout the bladder, trigone sparing in iOAB patients, trigone inclusive (5 in the trigone, 15 outside the trigone) for nOAB ones who need CIC.[71]

Statistical analysis

Data were collected using Microsoft Excel (version 12.2.4) and analysed with SPSS (version 22.0). Statistical differences in means were determined with t-tests; the significance level was set at $p<0.05$.

Results

The mean age was 60.0 years. 2 patients (5%) had early adverse effects after injection (1 vomiting, 1 pelvic pain), 4 (10%) needed CIC at 3 months, 1 of them also at 6 months (they were among the 8 neurological patients who underwent 200U dose). 38 (95%) answered positively to the questionnaire.

Botox® treatment showed a reduction in urinary leakage at 3 and 6 months after medical therapy failure and surgical procedure, and a significant lowering of Pdet at 6 months ($p<0.05$). Both 100 U and 200 U doses proved to be effective up to one year after toxin injection ($p<0.05$).

The side effects at 3 months were 1 haematuria and 3 UTI - 1 also recurred at 6 and 12 months - there was no statistically significant difference with oral drugs.

Table 1 shows results.

Table 1: Parameters registered pre- and post- botulinum toxin a injection.

N = 40 patients	Before therapy (medical and surgical)	After 3 months	After 6 months	After 12 months	After 24 months	p<0.05
Urinary leakage	36	6	4	8	16	<0.035 (3) <0.022 (6)
CIC	20	4	5	6	16	<0.038 (3)
Mean Pdet	45	15	12	14	30	<0.037 (3) <0.042 (6)
Adverse reactions	-	4	1	5	20	>0.05

NR = not recorded

Discussion

We believe that every correct approach to a disease goes step by step and certainly starting from the least invasive, from this point of view we agree on the fact that primarily OAB is correctly diagnosed by urodynamic examination and then treated primarily with life-style and physiotherapy, starting a medical therapy in conjunction with or immediately after the ineffectiveness or partial effectiveness of the conservative behavioral treatment; pelvic floor physiotherapy can be considered also.[4;72-87]

If the medical therapy has not had the desired effect, we perform the intratrusor treatment with botulinum toxin, which has been shown to have good efficacy.[88-93]

We think it is safer to perform this procedure in the face of a negative urine culture, although Bickhaus they stated that performing a first injection of onabotulinum toxin A within 30 days of urinary tract infection does not increase the odds of post-procedure urinary tract infection.[94]

Huang showed that intradetrusor injection of onabotulinum toxin A at the time of HoLEP is safe and is associated with improved urinary incontinence scores and AUA Symptom Score.[95] We performed toxin injection after the endoscopic disobstructive prostatic operation, because sometimes we observed the patient for persistent LUTS after the operations or to wait till the complete resolution of inflammatory field.

Chugtai assessed the efficacy of onabotulinumtoxinA (BOTOX, Allergan Inc., Irvine, CA, USA) in patients with refractory overactive bladder (OAB) after treatment for benign prostatic hyperplasia (BPH), although improvements in QoL were not statistically significant.[96]

Moussa demonstrated that intraprostatic injection of botulinum toxin A as modality treatment of LUTS/BPH significantly improved IPSS, Qmax, PVR, and decreased prostate volume.[97]

Similar results were reached also by Totaro and Ding.[98-99]

We have decided to administer 100U, while 200U have been injected in neurological patients. Abdelwahab highlighted that 100U injections seemed to have comparable results with 200U.[100] Arnouk randomized 2 groups of men with symptomatic BPH who failed medical treatment to receive 100U or 200U of BoNT-A into the prostate; the International Prostatic Symptom Score (IPSS), maximum flow rate (Q(max)), post-void residual volume (PVR), PSA levels and prostate volume before injection and after 3 and 6 months were evaluated. It was demonstrated that both doses produced significant improvements in IPSS, Q(max) and PVR after 3 and 6 months and both doses promoted comparable effects. Prostate volume was affected by 200U BoNT-A injection only after 6 months of treatment. PSA levels were significantly affected in the 100U group only after 6 months of treatment. In the 200U group, PSA levels were significantly decreased after 3 and 6 months. The complication rate was similar in both groups.[101]

The effectiveness of using this therapy has also been studied in cases following other surgical procedures, such as midurethral sling in women.[102]

The use of botulinum toxin A has been shown to improve urodynamic outcomes and the quality of life of patients, however its efficacy lasts up to a certain period and this must lead to the creation of a sort of programme/calendar with reminders of the treatment, stratify them according to the patients and anticipating the more complicated ones such as neurological ones.

Even if they were patients with prostatic hyperplasia, our population was quite heterogeneous, and this can be a pro to the extent that we have seen that the therapy is effective on neurological patients or not, a limitation can be given by the small number of the sample and by not having considered other parameters such as race or different surgical endoscopic operations or if they had undergone physiotherapy or other types of minimally invasive therapy before.

Conclusion

In general Botox® seems a valid therapeutic option for OAB patients, in particular after medical therapy failure. 100U appears as

an effective dose, but we prefer to use 200U in patients with neurological diseases. There were no clinical relevant differences between the doses, however a loss of effect is observed after 12 months the last intradetrusorial injection; this means that the treatment must be repeated after about one year, and possibly anticipated in neurological patients. Intradetrusor injection of 'onabotulinum toxin A' can be applied also in men affected by BPH who have previously undergone endoscopic prostatic surgery. Other clinical detections and considerations should be assessed in the next future.

Ethical Statements

All 40 patients signed an informed consent declaring to have understood the purposes, benefits, and risks of the proposed treatments.

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Conflict of interest

None.

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