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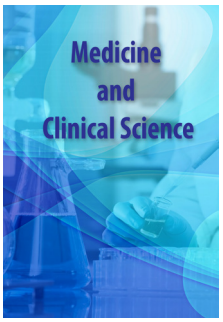

Assessing Effectiveness of 'Onabotulinumtoxin A' (Botox®) Intradetrusor Injection for Overactive Bladder Patients After Medical Therapy Failure

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Introduction

Urge Urinary Incontinence (UUI) is a common and chronic debilitating condition that impacts both the quality of life (QoL) and the economic aspects of patients and health care systems. Its prevalence among the male population ranges from 40% to 80% and it is defined as urine loss concomitant or immediately following an urgency episode. The most common symptoms associated with the condition are irritative lower urinary tract symptoms (LUTS) such as urgency, increased frequency and nocturia [1].

UUI shall not be misinterpreted as a synonym for overactive bladder (OAB), of which UUI is a common but not exclusive symptom. OAB is defined by the International Continence Society (ICS) as urinary urgency, usually accompanied by increased daytime frequency and/or nocturia, with UUI (OAB-wet) or without (OAB- dry), in the absence of UTI or other detectable disease [2]. According to the ICS, detrusor overactivity (DO) is defined as: 'a urodynamic observation characterized by involuntary detrusor contractions during the filling phase which may be spontaneous or provoked' [3]. Although the etiology of OAB is not well known, all theories highlight the role of the DO, suggesting that the sensory mechanisms of the bladder are compromised, leading to the creation of an 'urgency' in emptying the bladder at smaller quantities than under normal conditions. Two categories of OAB have been identified: idiopathic (iOAB) and neurogenic (nOAB), based on the etiological process underlying the condition [4].

The diagnosis of OAB is challenging and usually begins with a thorough history taking that aims to differentiate and quantify storage, voiding, and postmicturition symptoms, as well as sexual, gastrointestinal, and neurological symptoms.

After failure of behavioral and anthicolinergic therapy, we can consider the intradetrusorial injection of 'Onabotulinumtoxin A' (Botox®).

Botulinum toxin type A (BTX-A) began to be used over 20 years ago for neurogenic (DO) and received US FDA approval for the treatment of iOAB in 2013.10 Phase 3 studies showed significant improvements in all symptoms of OAB, with a consistent reduction in voiding frequency and dry rates reported in up to 23% of patients [5].

Botulinum toxin is a potent neurotoxin produced by Gram-negative anaerobic bacteria Clostridium botulinum. It inhibits calcium-mediated release of acetylcholine vesicles at the presynaptic neuromuscular junction acting on peripheral cholinergic nerve endings [6]. Seven serologic forms of botulinum toxin exist, but serotype A is the most commonly used for medical applications [7]. Around 12 weeks after the BTX-A injection, the lateral nerve endings are being formed, the renervation process in the denervated muscles starts and the muscle regains the ability to contract. This explains the short duration of the BTX-A effect. Besides, frequent administration of BTX-A at short intervals and the use of high doses facilitates the production of antibodies to BTX-A [8].

Materials and methods

We studied 62 patients between March 2019 and March 2021 (38 females and 24 males), previously treated with oral drugs (anti-muscarinic and/or beta-3 adrenergic), 14 of these had pathologies - 8 of them neurological. These last patients were injected by 200 U, all the others (52) by 100 U - 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.

The aim of our study is 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.

Surgical technique

The patient is placed in the lithotomy position. A gentle OTIS urethrotomy is performed if necessary. Rigid cystoscope is posi¬tioned and

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a 22G needle is inserted into the bladder wall and with¬drawn 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 62.5 years. 3 patients (5%) had early adverse effects after injection (1 vomiting, 2 pelvic pain), 5 (8.3%) needed CIC at 3 months, 1 of them also at 6 months (they were among the 8 neurological patients who underwent 200 U dose). 56 (93.3%) 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 100 U and 200 U 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 3 UTI - 1 also recurred at 6 and 12 months - there was no statistically significant difference with oral drugs.

Conclusions

Botox® is a valid therapeutic option for OAB patients. 100 U appears as an effective dose, however after 12 months it seems to lose its effect. There were no clinical relevant differences between 100 and 200 U doses. Engineered modified or liposomal botulinum toxins could represent novel more effective therapies over time.

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