

Original Research

The Role of Botulinum Toxin Type A in Neurogenic Overactive Bladder Dysfunction in MS Patients

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ABSTRACT

Introduction

Lower Urinary tract symptoms are common in patients with multiple sclerosis (MS) and have a negative influence on the quality of life (QoL). Detrusor overactivity is the most frequent symptom. Lifestyle modifications are the first therapeutic line followed by oral medication in patients with storage dysfunction. When these drugs are ineffective or intolerable, botulinum toxin bladder injection is an alternative treatment. The aim of this work is to evaluate the effectiveness and the impact on QoL of patients with MS and refractory or intolerant to oral therapy overactive bladder (OAB) after botulinum toxin type A bladder injection.

Materials and Methods

Retrospective study with six-months follow-up of patients with MS diagnosis and a refractory or intolerable to oral drugs OAB treated with botulinum toxin injections. All patients completed urological evaluation and a QoL questionnaire prior to the injection, 3 and 6-months after. Evaluation of the urodynamics tests prior and 3-months post injection was made.

Outcomes

Sixteen patients were treated. The QoL questionnaire showed progressive improvement 3 and 6-months after the injection. There was decrease in the number of daily voids urination and in the urinary incontinence episodes. There was an upgrade in the bladder capacity from 191 to 338 ml average (p 0.0004) and 75% evidenced disappearance of detrusor overactivity (p 0.0005). Thirteen (13) patients (81.25%) made spontaneous urination with post-voiding residue <100 ml after injection. Three (3) episodes of urinary tract infection were evidenced.

Conclusion

Botulinum toxin generates a positive impact on the QoL of patients with neurogenic OAB with MS.

Keywords

Overactive bladder; Multiple Sclerosis; Botulinum toxin.

INTRODUCTION

Multiple sclerosis (MS) is the most common progressive neurological disorder of young people. The average age of start is 30-years-old and a prevalence of 108 cases per 100.000 people in Europe.¹ It has a progressive course and there are four types of MS. The relapsing-remitting is the most reported, in about 85%. There are a lot of different symptoms consequence of the central nervous system demyelination and the subsequent altered nerve conduction.

The presence of urinary symptoms is really frequent with a prevalence of 37-99% for OAB syndrome, characterized by storage symptoms. For voiding symptoms the prevalence is 34-79% and for chronic urinary retention is 25%.⁴ Women are affected twice as commonly as men; however, men usually have a worse clinical presentation. The most frequent voiding disorder is spastic bladder and neurogenic detrusor overactivity.⁵

The International Continence Society (ICS) define the OAB Syndrome as urinary urgency, usually with an increase of frequency and nocturia, with or without urinary incontinence.^{6,7}

Urological involvement can condition the long-term prognosis of the disease due to the development of infections and renal complications. Thus, the correct diagnosis and treatment in these patients can provide greater control of the disease as well as, provide a better quality of life (QoL).⁸

The standard treatment of patients with overactive detrusor are the antimuscarinics drugs (also known as anticholinergics), which act blocking parasymphathetic nerve impulses to the detrusor muscle, making it relax and thereby improving bladder capacity. Beta-3 adrenergic drugs are also prescribed for these patients. Their mechanism of action is the stimulation of sympathetic receptors with the same purpose. Lack of response is not infrequent and the adverse effects of anticholinergics such as xerostomia, constipation, blurry vision, among others, often lead patients to abandon the treatment.

Despite this, anti-cholinergics or beta-3 adrenergics are the first line of pharmacological treatment for neurogenic OAB syndrome.⁹

There are some alternative treatments such as bladder injection of botulinum toxin type A, tibial nerve stimulation, pelvic floor kinesiology, sacral nerve modulation and surgery.

Botulinum toxin type A blocks the release of acetylcholine at the neuromuscular junction and leads to temporary chemodenervation of the bladder. Motor effects on the bladder have been studied extensively, leading to approval by the US Food and Drug Administration (FDA) in August 2011 for the treatment of refractory neurogenic OAB in patients with MS and spinal cord injury.

In those patients' intolerant or refractory to oral drugs, we investigated the effectiveness of endovesical therapy with injection of botulinum toxin type A into the detrusor.

To evaluate the effectiveness and impact of the botulinum toxin type A on the quality of life of MS patients with neurogenic overactive detrusor, who are intolerant of or refractory to oral therapy.

MATERIALS AND METHODS

Data from the medical records of all patients diagnosed with neurogenic OAB with MS defined by neurologists, refractory and/or intolerant to oral medical therapy with anticholinergics or B3 agonists dopaminergics, who received endovesical therapy with botulinum toxin in the Urology department of the Churruca-Visca Medical Complex from January 1, 2016 to January 1, 2019 were retrospectively analyzed.

The inclusion criteria were patients with diagnosis of MS with OAB were considered, with postvoid residual less than 1/3 of

their bladder capacity and without a history of recurrent urinary infections, negative urine culture at the time of the procedure and none were self catheterising.

All patients had a 6-month follow-up and completed a urological evaluation consisting in anamnesis, physical examination, 24-hour voiding diary, urine culture, renal function, renal and bladder ultrasound, and urodynamic study.

The urodynamic study was carried out according to the "Good Urodynamic Practices" recommended by the International Society of Continence with the Urodynamic ECUD[®] team from Medware Argentina.

An overactive bladder evaluation questionnaire (PotenzianiQol/VH-26) was performed. The Potenziani scale is a quality of life self-questionnaire related to urinary problems, initially developed for patients with spinal trauma and its validation has been extended to patients affected by MS.

It has 26 items which measure the affectation of the urinary disorders in four specific domains and their impact on quality of life: Frequency, Urgency, Incontinence and Nocturia. Each item has a response scale from 0 to 2 points, 0 indicates the absence of impact on quality of life and 2 means a severe affectation. The total score is represented by the sum of each item, being a low impact from 0 to 10, moderate from 11 to 26 and severe from 27 to 52 severe.¹⁰

Patients were informed about the endovesical botulinum toxin administration technique and its adverse effects, highlighting the possible need for subsequent intermittent catheterization. Informed consent was signed.

Endoscopic injection was performed according to the technique proposed by Schurch et al. Under antibiotic coverage according to antibiogram, in lithotomy position, under neuroleptoanalgesia and using a Prostaject[®] needle with a 19 Fr Storz cystoscope. 200 IU of onabotulinumtoxin A diluted in 20 ml of physiological solution were injected, distributed in 20 puncture sites of 1 ml each distributed on all sides of the bladder but respecting the trigone.

After the application, we again carried out the quality of life and overactive bladder questionnaire (PotenzianiQol/VH-26) at 3 and 6-months respectively, as well as a urodynamic study at 3-months.

The information was saved in the excel database and later analyzed using the statistical package Stata 13.0. The sample was described with measurements of central tendency and dispersion for the numerical variables and percentage for categorical ones. The comparison between the baseline data, at three and six months for the different variables were analyzed using the Wilcoxon test. For the comparison of the related variables, McNemar test was used. Statistical significance was considered with $p < 0.05$.

The protocol was evaluated and approved by the

Churruca Visca Medical Complex bioetichs committee.

OUTCOMES

Between January 1, 2016 and January 1, 2019, 16 patients diagnosed with OAB with MS intolerant or refractory to medical therapy were treated with botulinum toxin (200 IU). 75% of patients were women. The average age was 45-years, with an age range of 19 to 62-years. All had previously received individual or combined medical therapy. The mean oral therapy time was 10.93-months (Table 1). Seven (7) patients had adverse effects: 5 presented with a dry mouth, and 2 with constipation. Only one patient discontinued medication due to cognitive impairment. Only one patient discontinued medication due to cognitive impairment.

Variable	Total (n=16)
Female n (%)	12 (75)
Age Average (range)	43.81 (19-62)
Time of tacking Anticholinergics Average (range)	10, 93 (6-18)

Solifenacin was indicated in 37.5% of the cases, darifenacin in 25%, combined treatment with anticholinergic therapy+b3 agonist in 31.25% and tolterodine in 6.25%, prior to Botulinum toxin therapy.

The quantification of symptoms using the QoL/VH-26 questionnaire showed a progressive decrease when comparing baseline values and those at 3-6-months after botulinum toxin injection with a result of 34.43, 24.06 and 17.5 respectively ($p < 0.0013$).

The average daily pre-botulinum toxin urination was 10.62. Improvement was evidenced in the daily voiding survey at 3 and 6-months with an average of 7.81 and 6.87 ($p < 0.0002$). The mean number of incontinence episodes was 3.37. After the injection, there was a decrease to 1.31 episodes at 3-months and from 0.75 at 6-months ($p < 0.0026$) (Table 2).

Variable	Pre-Botox	3-months	6-months	p
QoL Average (range)	34.43 (17-50)	24.06 (11-38)	17.5 (8-27)	0.0013
Daily voidings (Number) Average (range)	10.62 (8-14)	7.81 (5-11)	6.87 (4-10)	0.0002
Urinary incontinence (Number of episodes) Average (range)	3.37 (2-6)	1.31 (0-3)	0.75 (0-3)	0.0026

*Firedman'sAnovatransformation test

In urodynamics studies, after an average of 12 weeks of application of botulinum toxin type A, we observed an increase in maximum cystometric capacity and an increase in bladder compliance.

Mean bladder capacity improved from 191 ml to 338 ml ($p < 0.0004$). In urodynamics, 12 patients (75%) did not evidence detrusor overactivity ($p < 0.0005$) (Table 3).

Variables	Pre- Botox	3-months	p
Overactive Bladder ¹ n=(%)	16 (100)	4 (25)	0.0005
Bladder Capacity ² (ml) Average (range)	191.25 (150-280)	338.75 (290-420)	0.0004

1. McNemar Test
2. Wilcoxon Test

Thirteen (13) patients (81.25%) achieved spontaneous voids with residues ≤ 100 ml, while 3 patients received catheterization for post-void residue greater than 100 ml.

Maximum efficacy was evidenced three-months after treatment. No systemic or local complications were observed. 68.75% of the patients, who were treated with botulinum toxin type A, were reapplied at least once more.

Three presented episodes of urinary tract infection in the 6-month follow-up period.

DISCUSSION

The general and long-term goals of treatment in patients with overactive bladder syndrome secondary to MS are to protect the upper urinary tract, achieve continence, and improve quality of life. Antimuscarinics remains the first line of treatment for overactive bladder after lifestyle changes.^{11,12} However, these medications have side effects that generate low adherence rates.

In a 2009 Cochrane review, the authors did not find enough evidence for the significant benefit of antimuscarinics in people with MS. In turn, high incidences of adverse effects were described in more than 1 in 5 participants.¹³ The findings of the review did not show significant differences between the different drugs.

The consumption of the medication reduces the sensation of voiding urgency, improves continence, and increases bladder capacity, mainly in the first months of use.¹⁴ Antimuscarinics have collateral effects such as dry mouth, constipation, among others. Oral mucosa dryness was reported in 1/3 of the patients with anticholinergic therapy,¹⁵ in our series we found similar results regarding mucosal dryness, being almost 32%, of which none abandoned therapy.

Currently, the evidence about the efficacy and safety of botulinum toxin is through randomized, placebo-controlled studies in which the authors evaluated patients with urinary incontinence and neurogenic overactive bladders of different etiologies, mainly spinal cord injuries and multiple sclerosis. There are few studies that include only patients with diagnosis of multiple sclerosis and OAB.

Botulinum toxin type A is the only type of botulinum toxin evaluated for the management of lower urinary tract dysfunctions through multicenter, randomized, controlled and randomized trials.^{16,17} Injections of botulinum toxin type A in the detrusor are highly effective in reducing the incidence of incontinence, in improving urodynamics parameters and, consequently, in the quality of life of patients.^{18,19}

Two double blind, randomized, placebo- controlled trials in patients with diagnosis of MS or spinal cord injury evaluated the difference between the doses of botulinum toxin (200-300 IU) without significant evidence on therapeutic efficacy of one over the other.^{18,20}

An important consideration when faced with a patient with neurogenic overactive bladder undergoing botulinum toxin therapy is the eventual need for clean intermittent catheterization after therapy, as it can affect bladder voiding.

In trials, 31.4% of patients with MS spontaneously voiding at baseline initiated clean intermittent catheterization after treatment with botulinum toxin,^{21,22} however this procedure does not affect the quality of life.^{22,23} In our work, 18.75% of patients (n=3) had to perform intermittent catheterization for the first time due to high postvoid residual volume, data similar to those provided by Mehnert et al.²⁴

Post-treatment urinary tract infections, are one of the most frequent complications with a reported incidence of 51.8 to 56%.²⁵ In our work, 18.75% of urinary infections were recorded. These patients may be those with higher residual volumes who started self-catheterization plan.

There are few studies on long-term follow-up of patients on therapy with botulinum toxin for neurogenic OAB. Baron et al²⁶ conducted a 10-year retrospective study looking for the reason for discontinuation of therapy. They showed that more than half of the patients with neurogenic overactive bladder abandoned therapy within 10-years, the main causes were therapeutic failures, patient decision, neurological condition progression and adverse events.

CONCLUSION

To conclude, botulinum toxin has a significant impact on the quality of life of patients diagnosed with multiple sclerosis with a neurogenic overactive bladder, being a safe and highly effective procedure, demonstrated in several trials in recent years. In our work, a significant improvement in the quality of life of patients could be evidenced, however, we consider the need for new trials with a larger sample size and prospective designs, with a longer follow-up time to obtain better levels of evidence.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We obtained the ethics approval.

AVAILABILITY OF DATA AND MATERIAL

The information was obtained from patient medical records.

FUNDING

There are no funding sources.

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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