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Efficacy of botulinum toxin in the management of refractory de novo overactive bladder symptoms in women after midurethral sling placement: retrospective, single center study

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Introduction This study aimed o evaluate the efficacy of onabotulinumtoxin A (onaBTX-A) intradetrusor injections in women with refractory de novo overactive bladder (OAB) following midurethral sling (MUS) placement.

Material and methods A retrospective single-center study was conducted. We screened 372 women who underwent MUS surgery between August 2009 and January 2022. 54/372 women diagnosed with pharmacologically refractory de novo OAB following MUS were evaluated using cystoscopy and urodynamics, and after tape erosion and obstructive voiding were excluded, they received onaBTX-A therapy. Outcomes were the reduction of self-reported OAB symptoms and leakage episodes, improvement of validated OAB scores and adverse events of the procedure after a follow-up of 3, 6, and 12 months.

Results Successful results were reported in 81%, 68%, and 43% at 3, 6 and 12 months respectively. Postoperatively, median voiding frequency and median nocturia episodes were significantly improved in 70% and 77% of women, respectively, with a decrease in daily number of voids (-4.1, p = 0.0001) and nocturia episodes (-2.2, p = 0.005). At 3 months, 80% of women reported an >25% reduction in urgency severity and episodes following injection. The median number of pads used was significantly reduced after injection (-2 pads; p = 0.03). Repeat injections of onaBTX-A were performed in 61% of patients after a median of 11 months.

Conclusions Intravesical onaBTX-A injections are clinically effective at 3- and 6-month follow-up for the treatment of refractory de novo OAB after MUS placement. Over 60% of the patients opted for retreatment with onaBTX-A due to a high level of satisfaction

Key Words: overactive bladder ‹› midurethral sling ‹› botulinumtoxin

INTRODUCTION

Stress urinary incontinence (SUI) is a very common health problem among women with significant negative impact on their quality of life (QoL). Currently, synthetic midurethral sling (MUS) placement is the most widely used minimal invasive surgical therapy of SUI when conservative management fails. Due to their high cure rates (62–98%), the number of MUS placement has increased substantially over the last decades, however, recently, their use has been paused in some countries following concerns about a variety of complications including pain, erosion, voiding dysfunction, sexual

difficulties, de novo prolapse and de novo overactive bladder (OAB) symptoms [1, 2, 3]. An estimated 4% to 17.2% of women treated with MUS will develop de novo OAB symptoms, including urgency, frequency and urge urinary incontinence (UUI) [4–8]. To date, there is limited data regarding the benefit of onaBTX-A specifically for patients with refractory de novo OAB following MUS placement [9]. Therefore, we aimed to evaluate objective and subjective success and safety of intradetrusor injection of onaBTX-A for patients with pharmacologically refractory de novo OAB following MUS placement

MATERIAL AND METHODS

This was a single-center retrospective study (ADVANCE) of the results of intradetrusor injection of onaBTX-A for patients with medically refractory de novo OAB following MUS placement. The Regional Ethics Committee for Medical Research approved the study protocol (vote number 2017-604-b-S). Study methods and definitions were applied according to the recommendations of the International Urogynaecological Association (IUGA) and the International Continence Society (ICS) [10]. All participating patients were counseled about the potential adverse effects of onaBTX-A and gave written informed consent.

A total of 372 women with SUI had received a MUS between 2009 and 2022 in our center. We identified and retrospectively analyzed 54 women with de novo OAB after MUS placement (tension-free vaginal tape (TVT)) refractory to anticholinergics who received intra-detrusor injection of onaBTX-A (Allergan, Irvine, CA).

Inclusion criteria were women with de novo OAB symptoms following MUS implantation, with at least one episode of UUI or urgency per day as documented in a voiding diary, who were willing and able to perform clean intermittent catheterization (CIC). At enrollment, all patients had been treated with anticholinergics for at least 3 months without sufficient improvement in de novo OAB symptoms or with treatment discontinuation due to adverse events. 3 patients wereWe excluded from the study due to urinary tract infection (UTI) via urinalysis and urine culture, preoperatively before applying onaBTX-A therapy. Women with preexisting OAB symptoms and/or urodynamically proven detrusor overactivity prior to MUS surgery, any grade of genital prolapse, history of pelvis irradiation, neurogenic bladder, significant voiding dysfunction following MUS or urethral/bladder erosion of the tape, were excluded from the analysis. An erosion was excluded through preoperative cystoscopy. To rule out voiding dysfunction, all women underwent preoperative (pre-botox) urodynamic testing by an experienced urogynecologist (first author) using a standardized procedure according to the recommendations of ICS [11]. Maximum uroflow of <15 ml/second, post-void residual (PVR) urine over 100 ml and bladder outlet obstruction index (BOOI) over 20 led to exclusion from the study. Collected data included patient demographics (age), previous pharmacological treatment for OAB, frequency of onaBTX-A injections, comparison of pre- and postoperative UUI, pad use, voiding frequency, nocturia episodes and reduction in urgency severity. Pre- and postoperative symptoms were assessed using the validated self-report questionnaire of the International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB). Urgency was assessed using the Patient Perception of Intensity of Urgency Scale (PPIUS), a 5-point scale ranging from 0 (no urgency) to 4 (urge incontinence).

Post-operative PVR urine, and the need for CIC were documented. Women were followed up routinely at 3, 6, and 12 months after injection treatment. A three-day voiding diary was routinely completed at baseline and at the 3-month visit to measure voiding frequency, nocturia, urgency and severity, and UUI episodes noted in the week prior to the follow-up visit. At each post-injection visit, PVR urine volume and subjective outcomes were assessed. A successful outcome was defined as a 25% reduction in urgency severity or UUI episodes [12]. The reporting of adverse events and the classification of the severity of events were documented using the Clavien-Dindo classification system [13].

Injection technique

All procedures were performed transurethrally under local anesthesia by the same experienced surgeon. 100 onaBTX-A units (U) were diluted in 20 mL of saline and given as 1 mL injections over 20 sites in the detrusor muscle including one trigonal injection. We used a 23-gauge injection needle in a rigid cystoscope (22 Fr). Women who developed acute urinary retention or a PVR volume greater than 150 ml underwent CIC to empty the bladder.

Statistical analysis

Statistical analysis was performed using IBM-SPSS v.19 for Windows (IBM Corp, Armonk, NY, USA). Descriptive statistics were used for the evaluation

of complication rates and the analysis of the questionnaire. The chi-squared test for trends can better assess if the success of the surgical procedure tends to decrease over time and the cure rates at the different follow-up visits (3, 6- and 12-month postoperatively). Changes in the number of incontinence episodes and the number of pads used were recorded in the ICIQ-OAB and PPIUS questionnaires, while bladder diary and pain scores were analyzed using the repeated, measured analysis of variance or the Friedman test, as appropriate. The Mann-Whitney U and Wilcoxon tests were used to compare ordinal and non-normally distributed continuous variables. The results were presented as medians, with range or means with standard deviation (SD) for normal distribution. The t-test was utilized for a comparison of the complications between the groups. At our sample size, we could reach the study power of 80%, so that the p-value below 0.05 was can be considered as statistically significant.

RESULTS

In a systematic review and meta-analysis, Fusco et al reported a success rate of 73.8% for SUI after MUS placement, but 50% also reported treatment of OAB symptoms after tension-free MUS placement [9]. Several studies have attempted to describe the possible different causative mechanisms of de novo OAB following MUS [10, 11, 12]. Intraoperative misplacement of the MUS close to the bladder neck, excessive tension on the tape, or gradual migration over time can ultimately cause secondary OAB due to obstructive voiding [13–15].

Anticholinergics and beta-3-agonists are currently the available pharmacologic therapies for idiopathic OAB [16]. However, the high cure rates of these pharmacotherapies for idiopathic OAB cannot be blindly extrapolated to de novo OAB, since the pathophysiological mechanisms and consequently the outcomes may differ significantly. A prospective study by Serati et al. showed that anticholinergic oral treatment with solifenacin for 3 months had significantly lower efficacy regarding urgency and UUI episodes in women with de novo OAB after MUS placement compared to female patients with idiopathic OAB [17]. Intradetrusal injections of onabotulinumtoxin A (onaBTX-A) have emerged as an alternative method for the treatment of refractory idiopathic OAB and in patients who cannot tolerate pharmacological treatment due to its side effects. OnaBTX-A injection therapy reduces the number of voiding, urgency, UUI and frequency episodes, increases cystometric bladder capacity, and significantly improves the QoL .

Demographic data including parity and body mass index (BMI) were analyzed as shown in Table 1. A total of 54 patients (14%) with mean age, 62.6 ±11.4 years who met the eligibility criteria were included in the analysis. According to clinical history and ICIQ-OAB questionnaires, all 54 patients had developed de novo OAB with increased frequency. The median duration of symptoms was 3.0 years (IQR: 1.6–7.0). Using urodynamic studies, 31 patients (57%) were diagnosed with detrusor overactivity (DO) and UUI. Conservative management of de novo OAB with oral anticholinergics had failed in 45 (83%) patients prior to onaBTX-A injection therapy. The remaining 9 patients (17%)

Table 1. *Baseline demographic and clinical characteristics of patients*

Variable	[all cases] N = 54
Age (years), median (SD)	62.3 ±11.4
BMI (kg/m^2), median (SD)	26.8 ±2.2
Previous hysterectomy, n (%)	18 (33,3)
Parity, median (SD)	2 ±1.5
Preoperative urodynamic investigation, n (%)	49 (91)
Detrusor overactivity, n (%)	18 (33)
Detrusor overactivity and de novo UUI, n (%)	31 (57)

SD – standard deviation; BMI – body-mass-index, UUI – urinary urge incontinence

Table 2. *Clinical symptoms before and after onaBTX-A injection*

Variable	Before onaBTX-A injection N = 54	3 months after onaBTX-A injection N = 54	6 months after onaBTX-A injection N = 38	12 months after onaBTX-A injection N = 38	p- value
Number of daily micturition/12 h, median (SD)	8 ±4	4 ±3	4 ±4	6 ±3,8	p = 0.0001
Number of nocturia, median (SD)	3 ±2	1 ±2	2 ±1	2 ±2	p = 0.005
Volume voided (ml), median (SD)	295 ±37.2	367 ±41	343 ±33	301 ±27.3	p = 0.001
Number on incontinence pads/24 h, median (SD)	3 ±1	1 ±1	1 ±2	2 ±1	p = 0.001

SD – standard deviation; onaBTX-A – onabotulinumtoxin A

had discontinued anticholinergic treatment due to adverse effects resulting from drug intolerance. The median duration of previous anticholinergic treatment was 11 months. The median time between MUS placement and the onaBTX-A injection was 6,5 years (SD: 1.9). At least one follow-up visit was completed in all patients, 38 patients (70%) completed two follow-up visits.

Efficacy and safety of onabotulinumtoxin A

Table 2 shows the clinical symptoms before and after onaBTX-A injection. After intradetrusor injection of onaBTX-A, 81% (44 of 54) of women were reported to be successfully treated at 3 months, 68% (37 of 54) at 6 months, and 43% (23 of 54) at 12 months. Repeat injections of onaBTX-A were administered in 33 patients (61%) due to recurrent de novo OAB symptoms with a median time to re-injection of 11 months (IQR: 7–19). The median number of onaBTX-A injection procedures was 4 (IQR: 3–7).

Three months postoperatively, median voiding frequency and median nocturia episodes were significantly decreased in 70% and 77% of women, respectively, with a median reduction in daily number of voids (-4.1, $p = 0.0001$) and median nocturia episodes (-2.2, $p = 0.005$). At three months following injection, 43 patients (80%) reported an >25% reduction in urgency severity and episodes. The median number of pads used was significantly reduced after injection (-2 pads; $p = 0.03$) the urge incontinence (UUI) episodes were reduced by 81% of women. The ICIQ-OAB score was reduced by 92% of women and the PPIUS was reduced by 91% of women. Postoperatively, two women (3,7%) had persistent large PVR urine requiring CIC for six weeks (Clavien-Dindo grade II). Uncomplicated UTI occurred in 6 women (11,1%) and was successfully treated with antibiotics (Clavien-Dindo grade II). No major postoperative complications were reported.

DISCUSSION

Transurethral intradetrusor injection of onaBTX-A is known to provide satisfactory midterm cure rates in women with pharmacologically refractory OAB or in women who are unable to tolerate anticholinergic drugs, without clinically significant adverse effects. Although onaBTX-A is a well-defined treatment option for patients with refractory idiopathic OAB [18–23], there is limited data on the benefit of onaBTX-A for refractory de novo OAB after MUS placement, which is ultimately derived from a single prospective series from Miotla et al. [9]. Therefore, although the European Association of Urology (EAU) Guidelines recommend onaBTX-A as a third-line treatment option for idiopathic OAB in patients who refractory to antimuscarinic or beta-3 agonist therapy, they do not include recommendations for the therapeutic regimen in de novo OAB after MUS implantation [13].

Miota et al. reported a significant decrease in the daily number of daily voids, UUI episodes and pads used ($p > 0.001$) as well as significantly increased mean voided volumes ($p > 0.001$) in both women with idiopathic OAB and de novo OAB following MUS treated with intravesical injection of 100 U onaBTX-A respectively, with no significant differences between groups. Regarding the safety of the procedure, increase of PVR urine volume was the most common adverse event in both groups, however, mostly asymptomatic, except for four patients with urinary retention, one with idiopathic OAB and three with de novo OAB. Two patients in the de novo OAB group (4%) required CIC for 1 month, and two (4%) developed UTIs [9].

These insights on de novo OAB following MUS are in concordance with our findings. Regarding the effectiveness of onaBTX-A injection, the current series show that up to 89% of patients undergoing the procedure benefit from the treatment by means of a significant reduction in their UUI, frequency and nycturia episodes, pad consumption and urgency severity. Regarding its safety, 3.7% of the cohort required CIC for six weeks and 11.1% required antibiotics due to UTIs, facts which indicate that morbidity through onaBTX-A is rare, similar to the idiopathic OAB [15, 16].

However, before initiating any pharmacological or onaBTX-A treatment for de novo OAB, obstructive placement and tape-specific complications such as erosion into the urethra or bladder must be ruled out, otherwise the tape should first be excised, and the obstruction removed before onaBTX-A injection. In our study, we excluded such complications through preoperative cystoscopy and urodynamic investigation using well established parameters, such as maximum uroflow (cut off value 15 ml/sec), PVR urine (cut off value 100 ml) and the bladder outlet obstruction index (BOOI), which was < 20 for all patients.

The main limitation of our study is its retrospective character, its relatively small sample size, as well as the absence of patients with idiopathic OAB as a control group, so a direct comparison regarding the onaBTX-A effectiveness in both forms of OAB is not possible. Consequently, a randomized study assessing the use of onaBTX-A versus placebo

in de novo OAB patients following MUS placement would be useful to validate our findings.

CONCLUSIONS

Based on the current findings, intravesical onaBTX-A injection significantly improves OAB symptoms such as urgency and frequency and reduces UUI episodes and pad use in women with refractory de novo OAB after MUS placement, indicating it to be an effective option after failure of oral pharmacological therapy for this patient group with a favorable safety profile.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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