Dysport Intravesical Injection in Patients with Neurogenic Detrusor Overactivity

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Abstract

Introduction and Objectives. OAB is bothersome for the patient, affecting the quality of life, but is also a burden to the public health systems. The primary aim of the treatment in neurogenic lower urinary tract dysfunctions is to protect the upper urinary tract. Secondary goals are to achieve urinary continence, to restore functions of the lower urinary tract and to improve the patient's quality of life. Intradetrusor botulinum toxin injections are recommended by the EAU as “the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity”, but as a third-line therapy for patients refractory to anticholinergic therapy. This treatment requires a prior urodynamic diagnosis of detrusor overactivity. Botulinum toxin, produced by Clostridium botulinum, works by blocking the efference of the reflex arc.

Materials and Methods. We performed a retrospective study which evaluated all NDO patients treated with Dysport in 2016 and 2017. A total of 47 patients were included in our study, aged between 24 and 67 years old, with either SCI or MS, 31 males and 16 females.

Results. The longest follow up available was 21 months. The significant reduction of incontinence episodes, which even disappeared in some cases is a great element of satisfaction for those involved and might lead to treatment compliance over time, with benefic results over other less evident parameters.

Conclusions. Abobotulinum toxin (Dysport®) is both safe and effective, and the results of our retrospective study are in line with data from the literature. Keeping in mind that botulinum toxin is not and should not become first line therapy, we should consider Dysport every time our initial treatment is not effective or well tolerated by the patient.

Key-words: botulinum toxin, Dysport, multiple sclerosis, neurogenic bladder, spinal cord injury, urodynamics

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Introduction and Objectives
The overactive bladder (OAB) is defined by the International Continence Society (ICS) as a syndrome characterized by urgency, with or without urgency incontinence, usually with increased daytime frequency and nocturia, in the absence of proven infection or other causative pathology \[1\]. The NOBLe study determined that OAB has a prevalence of 16.5% in the USA \[2\], while the EPIC study, performed over five countries in Europe, showed a prevalence of 11.8% \[3\]. OAB is bothersome for the patient, affecting the quality of life, but is also a burden to the public health systems.

While OAB is a clinical diagnosis, detrusor overactivity (DO) diagnosis implies urodynamic studies. The ICS defines DO as involuntary detrusor contractions during the filling phase, spontaneous or provoked. Additionally, DO is divided into Idiopathic Detrusor Overactivity (IDO) - when the cause cannot be determined, and Neurogenic Detrusor Overactivity (NDO) - when the underlying cause is a neurological condition. Whether to perform urodynamics or not and the timing are also debatable. The European Association of Urology (EAU) \[4\] recommends that urodynamics should not be done before trying the conservative treatment for uncomplicated urinary incontinence (gr. B), unless the findings may change the choice of invasive treatment (gr. B). As for neurological patients, urodynamics is necessary to document the (dys)function of the lower urinary tract (gr. A), with video-urodynamic being the gold standard (gr. A) but should definitely not be done before performing non-invasive testing (gr. A) \[4\]. NICE guidelines recommend dividing the neurological patients into two categories and to perform urodynamics on those at high risk of renal complications (spinal cord injury, spina bifida), but not on those with low risk of renal complications (most patients with multiple sclerosis) \[5\]. Most frequently, NDO is diagnosed in patients with Spinal Cord Injury (SCI) and Multiple Sclerosis (MS), even though the range of neurological diseases that associate NDO is actually wider: transverse myelitis, myelomeningocele, Parkinson’s disease, stroke, cerebral palsy, diabetes mellitus and several others.

Materials and Methods
The primary aim of the treatment in neurogenic lower urinary tract dysfunctions (NLUTD) is to protect the upper urinary tract. Secondary goals are to achieve urinary continence, to restore functions of LUT and to improve the patient’s quality of life as per the EAU guidelines. The non-invasive conservative treatment consists of assisted bladder emptying, behavioral modification techniques, LUT rehabilitation through electrical stimulation, use of external devices such as condom catheters and incontinence pads, and oral therapy.

Antimuscarinic drugs are first-line treatment and their effect is to normalize the intravesical pressure and increase cystometric bladder capacity \[6\] by binding to muscarinic receptors and making the detrusor refractory to parasympathetic stimulation. Oxybutynin chloride, trospium chloride, tolterodine tartrate, propiverine and darifenacin have proven to be both safe and effective. EAU recommends using a combination of antimuscarinic agents to maximize the outcome (LE 1a). Side effects, such as dry mouth and constipation, are one of the reasons patients discontinue the treatment. To lower the rate of dry mouth, extended release formulations can be used instead of immediate release ones \[7\]. Yet, withdrawal rates still reach 43% to 83% within the first 30 days of treatment \[8\].

Mirabegron is a beta-3 adrenoceptor agonist with level 1 clinical efficacy in treating OAB. Although the prevalence of side effects is similar to placebo \[9\] and the compliance is higher than in patients taking antimuscarinics (64.5% for mirabegron vs. 18.6% to 49.2% for the various antimuscarinics \[9\]), NICE recommends mirabegron as third-line treatment, for patients with a trial of at least two anticholinergics failed.

Alpha-blockers may decrease bladder outlet obstruction, residual urine and autonomic dysreflexia in SCI patients, so EAU considers it a grade B recommendation because not enough good quality evidence is available.

Minimal invasive treatment refers to catheterization, intravesical drug treatment, intravesical electrostimulation and botulinum toxin injections. Intermittent catheterization is the gold standard for the management of NLUTD, in case of detrusor underactivity or detrusor overactivity that can be controlled. With 4 to 6 catheterizations per day, so that the bladder volume does not exceed 400 mL, the risk of UTIs is greatly reduced.

Intravesical treatment with anticholinergics is supposed to minimize the systemic side effects, while the vanilloids capsaicin and resiniferatoxin desensitize C-fibers involved in detrusor overactivity. The effect of capsaicin lasts more than 6 months, and that of resiniferatoxin up to 12 months, with clinical benefits and improvement of urodynamic parameters superior for the latter \[10\].

Intradetrusor botulinum toxin injections are recom-
mended by the EAU as “the most effective minimally invasive treatment to reduce neurogenic detrusor overactivity” (gr. A), but as a third-line therapy for patients refractory to anticholinergic therapy. This treatment requires a prior urodynamic diagnosis of detrusor overactivity. Botulinum toxin, produced by Clostridium botulinum, works by blocking the efference of the reflex arc, inhibiting the release of acetylcholine into the neuromuscular junction and inducing a flaccid paralysis of the detrusor. It could also reduce sensitivity of C-fibers involved in the overactivity of the detrusor \[11\]. The effect is reversible. Out of the seven types of toxin, only types A and B have medical uses. For neurogenic detrusor overactivity, onabotulinum toxin A is the only FDA approved type, but abobotulinum toxin A has been used off-label for several years as well \[12\].

**Our study**

We performed a retrospective study which evaluated all NDO patients treated with Dysport in 2016 and 2017. As a general feature, all included patients were refractory to antimuscarinic treatment, which was taken for at least three months after the initial presentation. The neurological condition behind NDO was either SCI or MS, confirmed by multiple neurological evaluations. At least one evaluation done in the first three months after the procedure was available, so safety and efficacy data could be obtained.

Urodynamics was performed in all cases before the procedure and at 2-4 months after. The urodynamics machine is a Medtronic Duet Logic G/2 device, using water filled 8 Fr catheters. For filling, we use saline at room temperature, and a filling rate of 20 ml/sec. The patients are examined in a lithotomy position. A filling cystometry or pressure-flow study was performed, according to the procedure recommended by the ICS. Detrusor overactivity was defined as any contraction occurring on the Pdet trace, after properly determining that the device is properly calibrated. The patient was asked to cough at the beginning of the procedure and every minute after that. We recorded parameters like infused volume at the first detrusor contraction, maximum Pdet, maximum cystometric capacity, any leakage during the procedure. Bladder compliance is determined by the software and is saved along with all other parameters. The number of incontinence episodes before and after treatment was analyzed separately, as it represents a very bothersome condition for the patient, while not being dangerous from the physician’s perspective. All adverse events observed by the physician or reported by the patient were also recorded.

All patients had a negative urine culture before the procedure and normal coagulation tests. A written informed consent was obtained, consistent with hospital and national regulations. Antibiotic prophylaxis was used in all cases.

Fig. 1. Urodynamic trace showing NDO

All patients, regardless of their way of voiding the bladder, were informed that clean intermittent catheterization (CIC) might be required after the procedure.

Data was analyzed using the unpaired Student’s t-test.

Fig. 2. The Dysport kit
Reconstitution of Dysport

The commercially available kit contains a vial with 500 Speywood Units lyophilized powder, that will be reconstituted with 20 mL of preservative-free 0.9% saline to yield a solution of 25 Units per 1 mL. In order to dissolve, the vial must be swirled gently. The reconstituted Dysport should be a clear, colorless solution, free of particulate matter, as recommended in the leaflet found in the box of the product.

Injection technique

The injection technique is still a hot topic in the community[13]. In our study, the patients were administered a transurethral anesthetic jelly prior to the procedure, then placed in lithotomy position. Using a rigid 21 Fr cystoscope with continuous water flow and a 36 cm flexible, reusable 22 Gauge, Luer lock needle, the solution was injected into the detrusor, in 20 sites radially distributed. A 12° optics was used. We injected 1 ml per injection site, leaving at least 1 cm between sites. The trigone was also injected, keeping the same 1 cm distance from the ureteral orifices. At the end of the procedure, 2 ml of saline were injected so the needle is flushed, and no active substance is wasted. The total operating time averaged 15 minutes, and the bladder was completely evacuated through the cystoscope at the end of the procedure. The intervention took place without any other type of anesthesia.

Results

A total of 47 patients were included in our study, aged between 24 and 67 years old, with either SCI or MS, 31 males and 16 females. The longest follow up available was 21 months.

24 patients in our series had one retreatment, indicated after reevaluating symptoms and confirming clinical complaints with another urodynamic investigation. The second injection took place 9 to 16 months after the initial one.

As a general remark, clinical efficacy was reported by the patient shortly after the injection, and no systemic reactions were observed. No case of acute urinary retention was reported in the subgroup of patients with spontaneous voidings. All patients reported some degree of improvement, but 22 (47%) of them became asymptomatic after the injection, both clinically and on urodynamics. Another group of 19 patients (41%) showed significant improvement. After retreatment, the patients showed similar results compared to the initial injection.

Most frequent adverse events in our series were hematuria and UTI. While hematuria subsided without any treatment, for UTI the patients were given antibiotics.

Incontinence occurrence decreased by an average of 3.3772 ± 1.318 episodes, with a confidence interval of 95% and a p value of 0.0017, which, by conventional criteria is considered to be very statistically significant.

On urodynamics, the results showed significantly improved parameters across the series. The reflex volume increased from 155.33 ± 63.96 to 254.06 ± 77.03 ml, with a confidence interval of 95% and a p value of 0.0002, which is considered to be extremely statistically significant.

The Pdet max showed a constant decrease across the series, and the t-test demonstrated a reasonable statistical significance with a p value at 0.0311. The values decreased from 42.60 ± 23.31 to 25.90 ± 23.85 cm of water. This can be considered as the most important positive effect of the treatment safety wise.

The most spectacular increase was that of the maximum cystometric capacity (MCC). Before treatment, the MCC averaged 223.63 ± 120.87 while after the injection the MCC had an average value of 361.08 ± 94.89 ml, with a 95% confidence interval. P value was 0.0004, being considered as extremely statistically significant.

Bladder compliance showed an overall improvement as well, but the statistics didn’t show significance (p=0.1751). Nevertheless, considering the overall im-
proved clinical and urodynamic parameters, the patients’ satisfaction and the low rate of adverse events, we consider that the lack of significance should not be seen as a drawback.

Conclusions
Abobotulin toxin (Dysport®) is both safe and effective, and the results of our retrospective study are in line with data from the literature. The lack of specific symptom scores can be a barrier for a standardized evaluation of patients’ satisfaction in this particular population, but the subjective reports are consistent with objective results measured by urodynamics.

Although bladder compliance didn’t show significant improvement after Dysport injection, all other parameters were significantly improved. The effect is beneficial not only on subjective symptoms but also on those parameters which are not always perceived by the patient but can be dangerous in the long run.

The significant reduction of incontinence episodes, which even disappeared in some cases is a great element of satisfaction for those involved and might lead to treatment compliance over time, with beneficial results over other less evident parameters.

Keeping in mind that botulinum toxin is not and should not become first line therapy, we should consider Dysport every time our initial treatment is not effective or well tolerated by the patient. The higher initial cost of this procedure is balanced by the long-term symptom relief and the high satisfaction rates reported by the patients.

References
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