4 Treatment Options in Patients with Overactive Bladder: The Invasive Management

Musco Stefania, Gemma Luca, and Del Popolo Giulio

4.1 Introduction

Overactive bladder syndrome (OAB) is defined *refractory* if symptoms persist despite at least two attempts of oral therapy with muscarinic receptor antagonists and/or β3-adrenergics [1]. Different minimally invasive interventional procedures such as intradetrusor injection of botulinum toxin, sacral neuromodulation (SNM), or posterior tibial nerve stimulation (PTNS) might be considered when oral drugs are not effective. Major reconstructive surgery may also be indicated when the above-mentioned less invasive and conventional treatments fail.

4.2 Botulinum Toxin

Botulinum neurotoxins (BoNT) are protein complexes produced by Clostridium botulinum, an anaerobic gram-positive Bacillus. BoNT inhibit the muscle contraction by interfering with the release of acetylcholine (Ach) from presynaptic terminals.

Nowadays it is mainly used as an injectable treatment, although new possible non-invasive routes are under investigation in some experimental and preclinical studies [2, 3].

M. Stefania (✉) · D. P. Giulio
Neuro-Urology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy
e-mail: muscos@aou-careggi.toscana.it; delpopolog@aou-careggi.toscana.it

G. Luca
Urology Department, Azienda Ospedaliero-Universitaria Careggi, Florence, Italy

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4.2.1 Molecular Structure and Mechanism of Action

Seven serologically different neurotoxins (types A-G) are produced by four strains/species of Clostridium botulinum. Each of the BoNT serotypes are subsequently divided into subtypes based on different aminoacid sequences and immunobiological properties. Neurotoxin A (BoNTA) is commonly used for urological indications. Specifically, five subtypes have been described [4].

When BoNT is endocytosed, the N-domain of the heavy chain translocate the light chain into the cytoplasm. Once in the cytoplasm, the light chain cleaves SNAP25 of the SNARE complex protein, inhibits the Ach release and reduces muscarinic receptor M2 in the nerve terminal causing the flaccid paralysis of muscle [5]. It has been documented that BoNT also interrupts the afferent signals by reducing receptor expression in the urothelium [6].

More recently an anti-inflammatory effect has been hypothesized. Specifically, a decrease of substance P and nerve growth factor in urine has been found after BoNTA injections. Again, a possible apoptosis induced by BoNTA could cause the reduction of vascular endothelial growth factor expression in urothelium which may contribute to the effectiveness of BoNTA in treating sensory urgency in OAB and/or interstitial cystitis/bladder pain syndrome [7].

4.2.2 BoNTA Intradetrusor Injection

BoNTA was initially introduced in the 1990s to treat sphincter dyssynergia in spinal cord injury patients. After positive results on its effectiveness in relaxing striated muscle, its use in neurogenic bladder was expanded to manage neurogenic detrusor overactivity refractory to antimuscarinics.

Currently, despite there being three subtypes of serotypes A commercially available: Onabotulinumtoxin-A produced by Allergan Inc. (Botox®), Abobotulinumtoxin-A produced by Ipsen Biopharm Ltd. (Dysport®), and Incobotulinumtoxin-A produced by Merz Pharmaceuticals GmbH (Xeomin®), only Botox® is approved for the treatment of OAB wet syndrome in both genders.

The standard dosage for urgency urinary incontinence (UUI) is 100 units (U) dissolved in 10 mL of saline and injected under local anesthesia or mild sedation by flexible or rigid cystoscopy in 20 different sites (0.5 mL per injection) distant about 2 cm from each other on the bladder wall, sparing the trigone [8] (Fig. 4.1).

4.2.3 BoNTA Efficacy

According to literature, patients treated with OnaBoNTA, showed a significant reduction of daily UUI in about 60–80% of patients after 12 weeks post-injection. Between 42% and 87% of patients reported complete continence after treatment. Additionally, quality of life (QoL) was substantially improved in 35–65% [9].

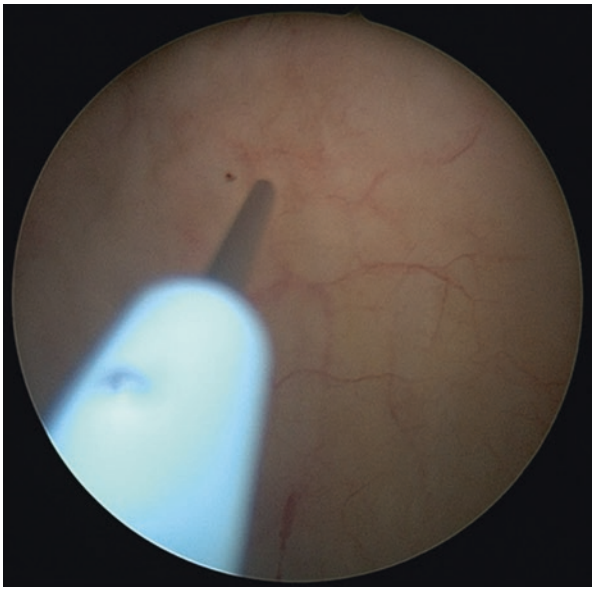

Fig. 4.1 Intradetrusor botulinum toxin A

OnaBoNTA has also shown to be more effective than muscarinic receptor antagonists in comparative studies [10]. A double-blind randomized study comparing OnaBoNTA 100 U or Solifenacin 5 mg vs placebo showed that incontinence reduction was significantly greater after Botox vs Solifenacin ($p = 0.022$) [11].

The median time of the duration of clinical response is 24 weeks. However, follow-up over 3.5 years showed consistent or increasing duration of effect for each subsequent treatment, with a median of 7.5 months [12].

4.2.4 Adverse Events

OnaBoNTA also proved to be generally safe for frail and elderly people [12]. A rate of about 25% of symptomatic urinary tract infection (UTI) has been recorded for OAB subjects who underwent OnaBoNTA [12]. Interestingly, a systematic review stated that the real rate of UTI is still unclear because of the wide heterogeneity and non-standardization of UTI definition [13].

Counselling revealed that the most dreaded complication for patients is the need for intermittent catheterization (IC) because of urinary retention (UR) which was described in about 8% of cases among the RCTs conducted for the OnaBoNTA approval process in OAB [9, 12]. Some consideration should be highlighted on this aspect. Firstly, the rate of urinary retention is associated with several factors such as age, gender (> men) and multiparity in women [14]. Finally, the risk of having to perform IC seems to depend on the ability to void before OnaBoNTA treatment. Osborne et al. showed that patients having post-void residual lower than 100 mL at baseline showed an extremely low risk for IC after OnaBoNTA (≤ 1%). Whereas

7/30 (23%) subjects with PVR > 100 and <200 mL started IC because of symptomatic urinary retention [15].

4.3 Sacral Neuromodulation (SNM)

Sacral neuromodulation was described for the first time by Tanagho and Schmidt about 50 years ago [16]. They demonstrated that a continuous stimulation of the sacral roots could modulate the lower urinary tract function during the micturition phase. Since then, several studies have shown the role this treatment has also had in other neurogenic and non-neurogenic pelvic dysfunctions such as pelvic pain syndrome, fecal incontinence, and constipation. InterStim® (Medtronic, Minneapolis, MN, USA) was the first implant approved by FDA for urgency urinary incontinence and/or urinary retention.

4.3.1 Technique

All patients who are SNM candidates for OAB may have a preliminary test phase (basic or advanced) to evaluate the harm and benefits of continuous stimulation.

A peripheral nerve evaluation (PNE) may be helpful to select patients and evaluate the integrity of the sacral plexus (basic evaluation test). A needle is placed percutaneously under local anesthesia on the S3 sacral root (Fig. 4.2). The motor and sensory response is evaluated during the anterograde stimulation through the needle. An anal contraction with a plantar flexion of the toe are indicative for a good motor response and integrity of sacral reflexes. The sensory response should be based on the type and site of sensation reported by the patients (anal, rectal, vaginal, scrotal, perineal). Both roots should be evaluated to see the best motor and sensory response (lower amplitude of stimulation). Subsequently a monopolar lead may be

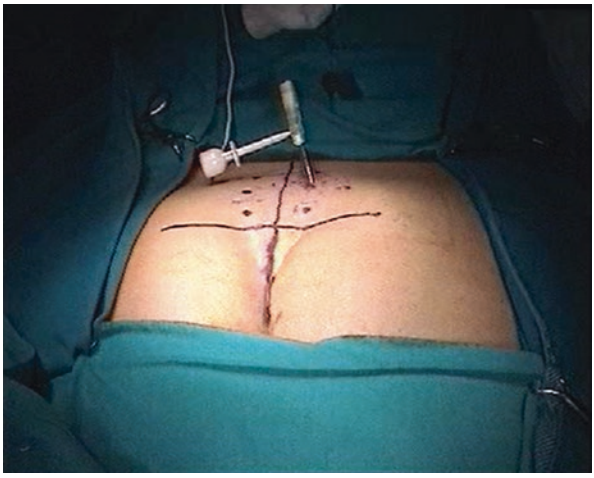

Fig. 4.2 PNE phase test—sacral neuromodulation

placed to evaluate clinical modifications during continuous stimulation. The lead must be removed within 14 days. The main disadvantage of this minimally invasive test is the high rate of false negatives (almost 50%) due to the easy displacement of the monopolar electrode [17, 18]. Therefore, in case of an unsuccessful test, patients should still have the chance to undergo the first stage of SNM (advanced evaluation test) to verify the PNE results or not.

During the first stage, a self-retaining quadripolar tined lead is positioned percutaneously on S3 foramen under X-ray guidance. This electrode is tunneled subcutaneously and connected to an extension cable which emerges from the skin, which in turn is attached to an external portable generator. As opposed to PNE, this test can be left in situ for up to four weeks. Another advantage of the first stage is the chance to optimize the clinical response by changing the stimulation parameters (mono or bipolar) in case of dissatisfaction during each scheduled or on-demand visit. Only patients with a significant clinical amelioration (at least >50%) should be implanted definitively with the internal pulse generator (II stage of SNM) [19].

4.3.2 Mechanism of Action

The exact mechanism of action of SNM is still unknown. One hypothesis is that it may have a direct anterograde action on the pudendal nerve but also retrogradely modulate the brain networks through the afferent pathways which may be somatic and/or visceral [20–22].

As a matter of fact, imaging and neurophysiological studies have demonstrated significant cerebral cortex activity when SNM is switched on. Moreover, it seems that the cortical areas involved by SNM are different depending on the time duration of stimulation [20]. With acute stimulation, a decrease in blood flow in the medial cerebellum and an increase in blood flow in the right postcentral gyrus cortex, right insular cortex, and ventromedial orbitofrontal cortex has been seen. Whereas, with chronic stimulation, changes in areas important for bladder awareness are more relevant (decrease in blood flow in the middle part of the cingulate gyrus, ventromedial orbitofrontal cortex, midbrain, and adjacent midline thalamus, and increase in blood flow in the dorsolateral prefrontal cortex) [22].

4.3.3 SNM Efficacy

According to evidence, SNM is a valid alternative option for wet OAB patients who are oral drug non-responders [23–25].

An RCT comparing the efficacy of SNM vs intradetrusor OnaBoNTA 200 U (*Rosetta* trial) in 260 including only women with wet OAB found that SNM was associated with a lower rate of cure and improvement at the first 6-month follow-up. Conversely, no significant clinical differences in terms of reduction of UUI episodes or resolution was seen at 24 months between both treatments. Again, changes in

patient reported outcome measures (PROMs) were also comparable at the 2 year follow-up [26].

Body mass index is considered a negative predictive factor of success for both types of treatments in women. Older age and a higher functional comorbidity index were associated with negative response, however, only in the group of women treated by OnaBoNTA ($p = 0.016$; $p = 0.031$, respectively) [27].

Considering the possible benefits of SNM on combined pelvic dysfunctions, it is worth mentioning that a recent supplemental analysis of Rosetta trial investigated the possible effects of OnaBoNTA or SNM on fecal incontinence and sexual dysfunction. Authors stated that no significant differences in Vaizey scores or sexual symptoms score measured by PISQ-12, and PISQ-IR were found [28].

Long-term success of up to 10 years has been confirmed by literature. Specifically, Al-zahrani et al. observed that almost two-thirds of UUI patients have maintained benefits [29].

4.3.4 Adverse Events

A lower risk of UTI has been seen after SNM compared to OnaBoNTA (10% vs 24%). The rate of revisions and/or SNM removal for failure was 3% and 9% respectively. . Regarding the risk of urinary retention, the same comparative study reported a lower rate of women starting IC (6%) despite the higher dosage of BoNTA injected (200 rather than 100 U) [26].

According to the *InSite* Study, 13% of the patients reported pain at the site of the internal generator. Almost one third underwent surgical revisions due to problems with the tined lead or battery change [25].

Currently, a rechargeable system, the Axonics® r-SNM is also available in some countries after FDA approval and CE mark, with similar safety and efficacy compared to the non-rechargeable SNM system [30, 31]. This has been designed to last at least 15 years with a mean interval of 7–14 days between charging depending on the parameter setting and amplitude of stimulation [32].

Currently Interstim® has also launched a full-body MRI compatible rechargeable or non-rechargeable system.

4.4 Percutaneous Tibial Nerve Stimulation

Percutaneous tibial nerve stimulation (PTNS) is the least invasive form of conventional neuromodulation recommended for OAB syndrome. The first FDA approved device for UUI was the Urgent PC® (Uroplasty, Inc., Minnetonka, MN). Another system called NURO® delivered by Medtronic has also recently become available on the market. PTNS should be offered to patients who are refractory and/or have poor tolerance to oral drugs and are unwilling to have more invasive treatments such as BoNTA or SNM.

4.4.1 PTNS Technique and Efficacy

The needle is placed in a traditional Chinese acupuncture site (Sanynjiao point, called also SP6), about 3–5 cm above to the medial malleolus and connected to an external generator. As the electrical impulse increases, the motor response mainly consists of toe flexion, whereas the sensory response is usually reported as a sensation along the sole of the foot and toe. The standardized SANS (Stoller Afferent Nervous System) protocol is 30 minutes of stimulation once a week for 12 weeks. Frequency is usually fixed at 20 Hz and pulse width of 200 μs [33].

Currently the efficacy of tibial nerve stimulation using transdermal pads or changing the parameter settings is still under investigation [34, 35].

Like SNM, the rate of efficacy after PTNS in improving storage symptoms and QoL in OAB patients ranges between 60% and 80%. Results in literature have been confirmed by comparative and sham-controlled studies [36, 37].

As regards urodynamics, the presence of severe detrusor overactivity has been considered a negative prognostic factor for PTNS success [38].

Despite the advantage of the less invasive treatment compared to SNM implant, the main limit of PTNS is still maintaining treatment and efficacy in the long term [39]. The initial clinical results on some definitive implantable devices which have been recently introduced on the market sounds promising [40].

4.5 Major Surgery

Very rarely do patients suffering from idiopathic UUI require major surgery. In according to the international guidelines, augmented cystoplasty could be offered as a last resort after all possible lesser invasive treatments have failed. Incontinent urinary diversion might be an option for those who are unwilling to empty their bladders by intermittent catheter and accept having to live with a stoma [41].

4.5.1 Enterocystoplasty

Ileum is commonly ileum preferred, considering that it is easier to resect and shape into a reservoir. Additionally, reconstructing the ileal transit is easier than using other portions of bowel (e.g., colon or stomach) [42] (Fig. 4.3).

Bladder preparation includes the removal of the supra-trigonal detrusor. The intestinal segment is usually resected at 25–40 cm from the ileocecal valve and it needs to be long enough to be shaped into a spherical form. It is extremely important to avoid any tension to the mesenteric vessels to prevent ischemia. The ideal size of the ileal segment is about 25 cm. Once the ileal reservoir is made, it can be anastomosed to the residual detrusor.

Comparing cystoplasty and intradetrusorial BoNTA, El-Azab et al. observed greater improvements in storage symptoms and QoL at 6 months follow-up in the

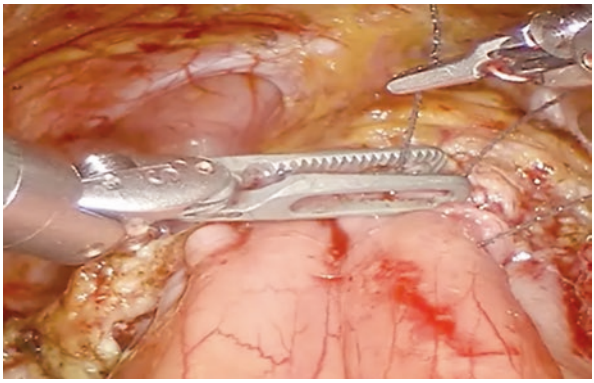

Fig. 4.3 Robotic-assisted ileocystoplasty

group of patients who underwent bladder augmentation. However, the same patients showed more voiding difficulties, and 26.7% required IC [43].

Besides the advantages and disadvantages of the different surgical techniques (open, laparoscopic, or robotic assisted), bladder augmentation carries several distinct long-term risks. A higher risk of urinary tract infections due to the colonic commensal bacteria colonization, mucus production, metabolic acidosis and bladder tumors can occur over years [42, 44].

Considering the risk of malignancies, long-term surveillance by cystoscopy is still controversial. In a recent systematic review study, the rate of malignancy after cystoplasty ranged from 0% to 5.5% and the estimated incidence ranged from 0 to 272.3 per 100,000 patients/year [45].

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