Chapter

Botulinum Neurotoxin Uses in Overactive Bladder

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Abstract

Botulinum neurotoxin has been approved for use in different urologic disorders, especially overactive bladder (OAB). OAB is highly prevalent, with a relevant impact on patients' quality of life and the available health resources. The prevalence of OAB is 11.8% with no significant difference between male and female. Botulinum neurotoxin is now approved as a treatment of choice for refractory overactive bladder (ROAB) after the failure of behavioral and pharmacological therapy. It is associated with improvement of urgency and urge urinary incontinence in 60–70% of patients. Yet the effect is not long-standing and fades out in a mean of 6-months duration and repeated injection is warranted. Moreover, its associated side effects are not uncommon, especially urinary tract infection and urine retention. New modifications have been studied to make it less invasive, effective, and tolerable by the patients through injection-free mode. The subject to be explained in the book chapter is the role of botulinum neurotoxin in ROAB, including the mechanism of action, different types of botulinum toxin used, the accepted dose, associated side effects, and comparison of the outcome to other available treatment modalities. In addition, a close look at the new accepted approaches for intravesical administration of botulinum toxin in the bladder will be done.

Keywords: botulinum neurotoxin, overactive bladder, refractory overactive bladder, outcomes

1. Introduction

The International Continence Society (ICS)/International Urogynecological Association (IUGA) defines overactive bladder (OAB) as urgency with or without urge incontinence (UUI), associated with urinary frequency and nocturia in the absence of pathological (e.g. UTI, stones, bladder tumor) and metabolic factors (e.g. diabetes) [1]. The diagnosis is made by exclusion. Whether there is nerve damage or not, OAB might be classified as neurogenic or idiopathic. The prevalence of OAB is 11.8% with no significant difference between male and female and the incidence increases with age [2]. The prevalence of OAB in adults aged ≥18 years was 16% in men and 16.9% in women in the USA, and in adults aged ≥40 years, it was 15.6% for men and 17.4% for women in Europe. In Asia, the prevalence of OAB was lower, but it was still 6.0% with no differences between male and female [3].

As a result, proper understanding and management of OAB is mandatory to improve patients' quality of life and decrease its socioeconomic burden. Behavioral therapy, bladder retraining, and pelvic floor exercise represent the first line of management of OAB. Pharmacotherapy is the second line of treatment. Anticholinergics and β3 agonists have been shown to be clinically effective in people with OAB [4]. Yet, it has many side effects such as dry mouth, dry eyes, constipation, blurred vision, dyspepsia, urine retention, and reduced cognitive function, which limit their use especially in elderly. More than 70% of patients discontinue medication within 6 months to 3 years due to side effects [5]. Refractory OAB (ROAB) develops when both behavioral therapy and oral medications become no longer effective [5]. The AUA/SUFU guidelines describe ROAB as a failure of behavioral therapy after 8–12 weeks and failure of at least one anticholinergic agent used for 4–8 weeks [6]. ROAB has an unknown prevalence rate, but it is not uncommon among the OAB population [7]. Third-line treatment should be considered when patients fulfill the ROAB diagnostic criteria. Sacral neuromodulation (SNM) and Botulinum neurotoxin-A (BoNT-A) have been recently demonstrated to be successful, with success rates reaching up to 60% and 70%, respectively [6].

BoNT-A is frequently used for cosmetic purposes and is used to treat strabismus, blepharospasm, muscle dystonia, hyperhidrosis, and migraine [8]. Carpenter was the first to prove that botulinum neurotoxin inhibits bladder contractility in rats in 1967. In 2011, BoNT-A was licensed for the treatment of urine incontinence (UI) caused by neurogenic overactive detrusors. The US Food and Drug Administration (FDA) approved it for the treatment of OAB in 2013 [9].

2. Pathophysiology and management of OAB

OAB is a chronic condition of urgency, frequency, nocturia with or without UUI. It is sub-classified into dry and wet type based on the absence or presence of the UUI. The exact cause of OAB is not well-understood. The pathophysiology varies between neurogenic, myogenic, or idiopathic factors [10]. The imbalance between the excitatory and inhibition neural pathway to the bladder is one of the underlying mechanisms. Also, the increased sensitivity of bladder muscle receptors and muscarinic receptor upregulation plays a role in OAB pathophysiology [11]. Another potential cause is the myogenic dysfunction secondary to structural or functional alteration of the detrusor smooth muscle. Idiopathic detrusor instability of undetermined underlying cause is another mechanism [10].

Proper history taking and at least a 3-day bladder diary are indicated for initial evaluation of patients in order to quantify OAB symptoms. Urodynamic evaluation is essential for establishing the diagnosis. The hallmark urodynamic feature of OAB is detrusor overactivity (DO). Yet, it may not be demonstrated in some patients due to the inability to reproduce symptoms during the urodynamic [12]. It is worth mentioning that urodynamic diagnosis has no proven predictive value for the treatment response [13]. And EAU guidelines recommended against routine urodynamic evaluation before starting the first line of treatment for uncomplicated OAB [14].

The first line of management is conservative treatment in the form of lifestyle modification (fluid restriction, decrease caffeine intake, weight reduction, and stop smoking), behavioral therapy, bladder retraining, timed voiding, and pelvic floor muscle exercise [14]. Bladder retraining and timed voiding work by setting a target time for using the toilet before it patient should not void. Once this is achieved the

time can be lengthened. Thus the central control can be re-learned as in infancy. Pelvic floor muscle training; described by Kegel, aims at strengthening and rehabilitating the pelvic floor muscle, increasing its tone, and increasing urethral resistance [15].

The second recommended line of treatment is pharmacotherapy. It can be initiated together with conservative treatment or postponed till the failure of conservative treatment based on the OAB symptoms severity. The EAU and AUA guidelines recommended anticholinergics and β3 agonists as a pharmacological treatment of OAB [6, 14]. Anticholinergics are competitive muscarinic receptors antagonists. They prevent cholinergic muscarinic receptors activation in the urinary bladder and consequently reduce spontaneous detrusor muscle activity during the filling phase and decrease detrusor pressure. Many anticholinergics have been used in clinical trials and none proved to be superior to the others in OAB management. Dose escalation may be appropriate in certain patients and increases the response [16]. The efficacy of anticholinergics varies between 50% and 75%. They help to reduce urgency and UUI episodes along with reducing frequency of micturition. However, adherence to anticholinergic treatment is low and decreases over time because of lack of efficacy, adverse events, and/or cost and a significant number of patients will stop anticholinergic agents within the first 3 months [17, 18].

When anticholinergics are ineffective, non-tolerated, or contraindicated, β3 agonist (mirabegron) can be used. It activates the β-3 adrenergic receptor in the detrusor muscle in the bladder, which leads to muscle relaxation and an increase in bladder capacity helping the bladder to fill and store urine. Yet, it is not free of side effects. Tachycardia, hypertension, dyspepsia, palpitations, atrial fibrillation, joint swelling, rash, and pruritus were reported with mirabegron use [19].

Patients who are refractory to behavioral and pharmacologic therapy should be properly reevaluated. If the diagnostic criteria of ROAB are fulfilled, a third-line treatment should be offered. Third-line therapy recommended by guidelines is intradetrusor injection of BoNT-A or sacral neuromodulation [6, 14].

3. Mechanism of action of botulinum neurotoxin

Botulinum toxin is a neurotoxin derived from Gram-positive, spore-producing bacteria (*Clostridium botulinum*). The bacteria produce seven serotypes (A–G) of botulinum toxin each with different antigenic profiles and biochemical actions; however, they all have a similar pharmacological effect [20]. Botulinum toxin types A (BoNT-A) and B (BoNT-B) have been developed for clinical use. BoNT-A has the longest duration of action which makes it more suitable for clinical use.

BoNT-A is synthesized as a single polypeptide chain (150 kDa) which is cleaved into a light chain (50 kDa) and a heavy chain (100 kDa) held together by a fragile disulfide bond and noncovalent bonds. The available formulations of BoNT-A are BOTOX (onabotulinumtoxin A) (Allergan, United States), Dysport (abobotulinumtoxin A) (Ipsen, United Kingdom), and Xeomin (incobotulinumtoxin A) (Merz, Germany). Each formulation of BoNT-A has its own dosing regimen which is not interchangeable. BOTOX is most commonly used followed by Dysport (the former is five times more potent than the latter) [20].

Although fibroblast growth factor receptor 3 has been mentioned as a potential BoNT-A receptor, two forms of BoNT-A cell-surface receptors have been identified: gangliosides and the synaptic vesicle-associated protein 2 (SV2) family [21]. BoNT-A's

heavy chain attaches to SV2 on the nerve terminals' surface, followed by endocytic internalization of the toxin within the nerve terminal. The toxin is broken within the synaptic vesicle after translocating into the cytoplasm, leaving the light chain of BoNT-A as the actual active moiety. BoNT-A light chain can then cleave synaptosome-associated protein (SNAP25) off the SNARE proteins, a complex protein that when intact forms the core of the neuroexocytosis machinery. This disrupts the fusion of neurotransmitter-containing vesicles with the neuronal cell membrane, inhibiting neurotransmitter release [22].

SV2-immunoreactive and SNAP25-immunoreactive nerve fibers are found in the sub-urothelium and muscle layer of the human bladder, but not in the urothelium. Almost all parasympathetic nerves express SV2 and SNAP25, while only about half of sensory and sympathetic nerves do [23]. Cleaved SNAP25 is the final product of the BoNT-A light chain's enzymatic activity. It is regarded as an appropriate marker of BoNT-A's action and, thus, an essential target in future research [24].

3.1 Motor effect of BoNT-A

Intradetrusor injection of BoNT-A temporarily blocks the presynaptic vesicular release of acetylcholine (ACh) at the neuromuscular junction of the parasympathetic nerves supplying the detrusor muscles and decreases detrusor pressures and phasic contractions in both idiopathic and neuropathic bladders. However, patients also report a significant decrease in urgency and hence, it is hypothesized that botulinum toxin also modulates the sensory pathways [20].

3.2 Sensory effects of BoNT-A

BoNT-A suppresses bladder sensations by processes unrelated to its effects on ACh release. Transient receptor potential vanilloid subfamily 1 (TRPV1) and P2X3 immunoreactive fibers can be seen throughout the sub-urothelium of the human bladder [25]. BoNT-A injection reduces TRPV1 and P2X3 activity in sensory nerve fibers with subsequent reduction in the frequency of urgency episodes [26]. Also, intravesical BoNT-A injections have been demonstrated to reduce ATP and neurotrophin release from urothelial cells and increase NO release [27]. ATP has been shown to play a role in the pathophysiology of OAB by mediating the sense of bladder fullness [27].

4. Techniques of administration of BoNT-A

Intradetrusor injection of BoNT-A should be offered to carefully-selected and thoroughly-counseled patients with ROAB not responding to the previous two lines of treatment. Patients should be able and willing to maintain close follow-up and frequent PVR estimation and accept the possibility of self-catheterization [6].

Patients should be given enough written and verbal peri-procedure instructions, as well as information regarding urinary tract infection (UTI) and urine retention. Prophylactic antibiotics are recommended for all patients and continue for 1–3 days postoperatively. Urinalysis should be performed before the procedure to rule out active infection. Administration of intradetrusor BoNT/A injections has been described in an office setting under local anesthesia or in the operating room with regional or general anesthesia using a flexible or rigid cystoscopy.

For idiopathic detrusor overactivity typically 100–200 units of BOTOX (diluted in 20 mL of normal saline) or 750–1000 units of Dysport have been used. BOTOX 100 U is licensed in Europe to treat OAB with persistent or refractory UUI in adults of both genders [14]. Similarly, the AUA guidelines recommended 100 U of BOTOX as a third-line of treatment of OAB [6].

There is no consensus on the ideal injection technique. The location of injections, the depth of injections, the number of injection sites, and the volume at each site vary in literature. Kuo et al. looked back at injection sites and discovered that success rates were the same whether they were in the bladder body alone, the trigone alone, or the bladder body and trigone together [28]. In a subsequent meta-analysis of OAB patients, no significant differences in efficacy between trigonal sparing and non-trigonal sparing injection techniques were found with short-term cure rates of 52.9% and 56.9%, respectively [29].

The injection depth varies as well and is influenced by the length of the needle tip (available tips range between 2 and 8 mm) used for injections. Some authors added a trace amount of indigo carmine or methylene blue to the injection solution to facilitate observation of the procedure and assessment of drug distribution [30]. Even among the same surgeons, there is likely to be some variation, and no study has determined whether sub-urothelial or intradetrusor injection is preferable. However, intradetrusor injections, as opposed to submucosal injections, with sparing of the trigone are favored. Again, there is no consensus on the number of injection sites and the dilution of the toxin but generally, 20 sites are injected and the volume per injection is usually 0.5–1 mL (**Figure 1**) [31].

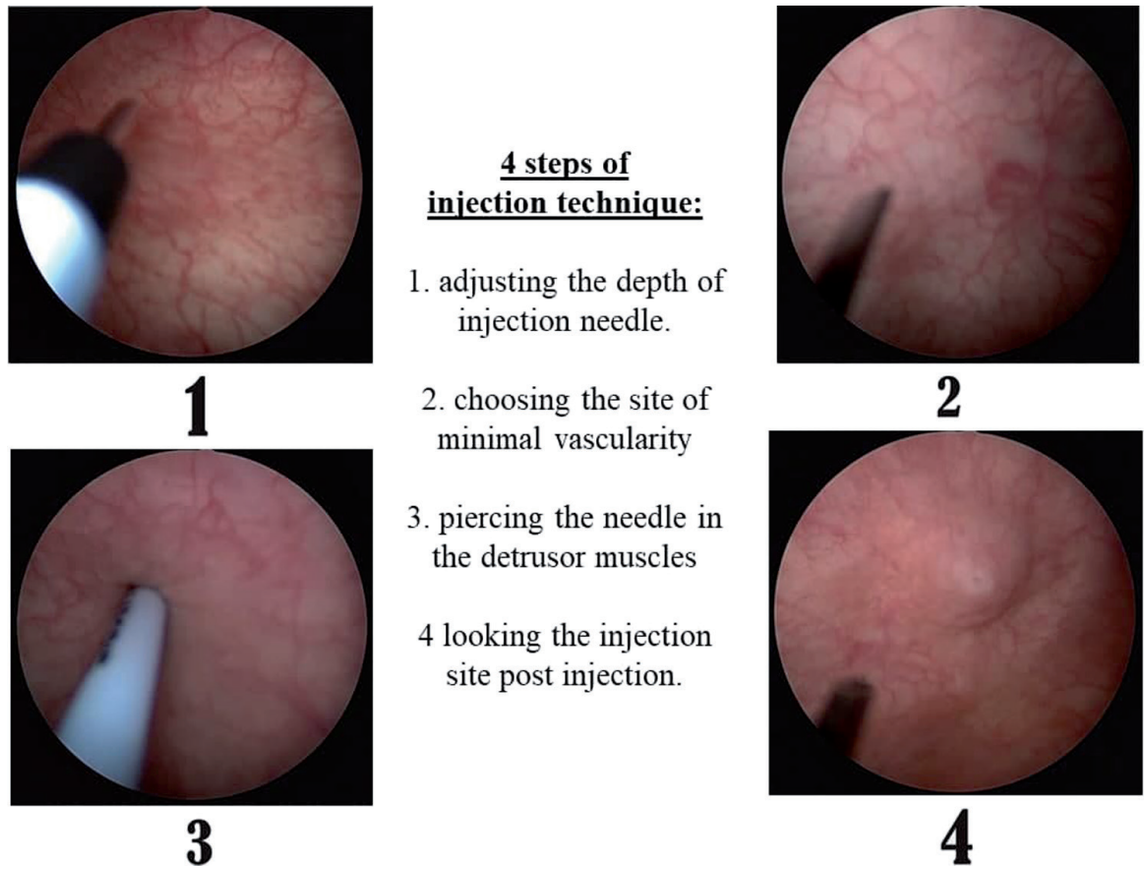

Figure 1.
Illustrate the technique of intra-detrusor injection of BoNT-A.

4.1 Precautions during injection

- Botox is a vacuum-dried protein that must be refrigerated. The vials must be reconstituted with preservative-free saline before injection, and the combination can be kept at 2–8°C for up to 24 h.

- It's worth noting that the product contains human albumin, which should be disclosed due to some patients' reactions to it [31].

- To avoid protein denaturation, avoid rapid shaking of the vial when preparing the combination. Developing an institutional method for labeling syringes containing botulinum toxin dilutions is a significant practical consideration, especially if nurses or other personnel are engaged in its preparation [31].

- Because the thickness of the detrusor muscle varies with the grade of bladder filling, puncturing the muscle appears to be very easy, especially at high bladder filling grades. Furthermore, the bladder wall between trabeculation bars might be quite thin and easily perforated. A suburothelial injection may be a viable option.

5. Efficacy of BoNT-A injection in ROAB

In a multicenter double-blinded randomized trial compared the efficacy of 50, 100, and 150 U onabotulinum toxin A to placebo in OAB patients, at 3 months >50% improvement in urgency and UUI was reported by 37% of the 50 U patients, 68% of 100 U patients and 58% of 150 U. Only the 100 U groups was statistically significant compared to the placebo group. Frequency was statistically significant, reduced in 100 and 150 U groups and complete continence at 3 months was significantly greater in the 100 U group (55%) and the 150 U group (50%) compared to the placebo group (11%). At five-months post-treatment, these differences were maintained [32].

A phase III trial randomized 557 OAB-wet patients; whose symptoms were not responded to anticholinergics to receive bladder wall injections with BoNT-A (100 U) or saline. At week 12, in patients treated with BoNT-A, UUI episodes were halved and the number of micturitions reduced by more than two. A total of 22.9% of the patients in the BoNT-A arm were fully dry, against 6.5% in the saline arm [33]. Tincello and colleagues published the results of the RELAX study including 240 women with refractory OAB to compare 200 U BoNT-A and placebo injections. At 6 months, voiding frequency, urgency, and incontinence episodes per day were significantly reduced in patients receiving BoNT-A injection. Continence was also significantly higher in the treatment group (31% vs. 12%, $p = 0.002$) with subsequent statistically significant improved patients' QOL [34].

In early systematic review assessing the efficacy and safety of botulinum toxin in the management of OAB, Anger et al. reported that BoNT-A treatment improved incontinence episodes and patients' QOL scores, as shown by a 15-point drop in Urinary Distress Inventory scores compared to placebo-injected patients [35]. In a recent systematic review and network meta-analysis, BoNT-A (100 U) had associated with the greatest reductions in urinary incontinence (UI) episodes, urgency episodes, and micturition frequency, and the highest odds of achieving decreases of 100% and ≥50% from baseline in UI episodes/day. In comparison to other pharmacotherapies, BoNT-A was more superior in reduction of UUI episodes, urgency,

and frequency and was associated with higher odds of achieving a 100% and ≥50% decrease in UUI episodes/day than most other treatments in the network [36].

Moreover, pre-treatment with BoNT-A improved patients' response to anticholinergic treatment. One hundred pre-treated patients with intravesical injections of 100 IU of BoNT-A and the effect faded, were randomized to receive 10 mg solifenacin and placebo for 12 weeks. After 12 weeks of follow-up, all overactive bladder symptom score items, including the total score, had improved significantly ($P < 0.0001$) in solifenacin group. Also, urodynamic parameters including frequency and amplitude of detrusor contractility and detrusor leak point pressure decreased significantly with increased cystometric capacity and improved incontinence quality of life parameters with solifenacin re-treatment [37]. This was explained by the possibility that repeated BoNT-A injections increased bladder capacity and restored the normal numbers and function of M3 receptors, potentially restoring patients' responsiveness to anticholinergic drugs [37]. This was based on the clinical findings and immunohistochemical assays which evidenced that BoNT-A injections could restore the number and efficacy of intra vesical urothelial and suburothelial receptors [38].

The effects of BoNT-A injection last for 4–10 months (mean 6 months). The median time to request re-treatment in the pooled analysis of the two RCTs was 24 weeks [33, 39]. Follow-up over 3.5 years showed the consistent or increasing duration of effect for each subsequent injection, with a median of 7.5 months [14].

6. Botulinum toxin injection-related adverse events

Intradetrusor injection of BoNT-A is still an invasive procedure and associated with a considerable incidence of adverse events. The local side effects include pain, UTI, bleeding, no benefit, need for further injections, need for temporary self-catheterization. The generalized side effects include flu-like symptoms, dry mouth, and malaise. Bauer et al. focused on side effects with botulinum toxin injection and reported that 54% of patients reported at least one side effect [40]. The side effects included urinary retention (8.9%), gross hematuria (17.9%), UTI (7.1%), dry mouth (19.6%), dysphagia (5.4%), impaired vision (5.4%), eyelid weakness (8.9%), arm weakness (8.9%), and leg weakness (7.1%). However, symptoms other than urinary retention and UTI were transient and resolved without the need for further treatment [40].

The reported rate of UTI ranged from 3.6% to 54.5% from different RCTs [6] and some reported increased rates of UTI with increases in the dose [41].

Increased PVR and the need for self-catheterization is not uncommon adverse event after botulinum toxin injection. The rate of urinary retention in published studies ranges from 5.4 to 43%, depending on how retention is defined [6, 20, 33, 39]. An interim analysis of a long-term extension study found that the proportions of patients requiring CIC remained stable at 4.6%, 4.1%, and 4.7% after one to three BoNT A treatment cycles, respectively [20]. The onset of urinary retention usually coincides with the onset of clinical efficacy, which occurs between 5 and 10 days after injection and the duration of retention varies, with some patients only requiring CIC for a few days, while others require CIC for the duration of the drug's effects [42–44]. Multivariate analysis revealed that preoperative PVR ≥ 100 ml and preoperative bladder capacity were associated with postoperative urinary retention for the first BoNT-A treatment. Preoperative PVR, BoNT-A units injected, and retention after the first injection were all associated with an increased rate of postoperative retention in those who received a second BoNT-A treatment [45].

Mild hematuria is expected to occur transiently after the procedure due to the injection technique, but severe hematuria requiring intervention or hospitalization for bladder irrigation occurs infrequently [44]. Not all patients benefit from treatment, and many patients discontinue injections outside of clinical trials due to a lack of efficacy or intolerable side effects, such as the need for catheterization [43].

7. Botulinum toxin versus SNM for ROAB

The choice between both BoNT-A and SNM for the management of ROAB is influenced by many factors. BoNT-A is a straightforward day case or outpatient procedure, which could be performed with local anesthesia or intravenous sedation. But it is still an invasive procedure. Also, due to the self-limited duration of action, reinjection every 6 months may be necessary. Whereas, SNM is more complex that necessitates a two-step procedure. However, its effect can last for 4–6 years or even longer. Currently, SNM associated risk of injury and surgical complexity are more tolerable due to the standardized and popularity of the technique. As a result, patients may prefer treatment with a longer duration [46]. Safety and effectiveness are critical factors to consider when making a decision. Efficacy and safety of BoNT-A injection and SNM are often assessed using successful treatment rates (symptoms of OAB improvement >50%) and adverse events,

	Sacral neuromodulation (SNM)	**Botulinum toxin (BoNT-A)**
Mechanism of action	SNM mainly functions in the central nervous system: • Somatic afferent nerve activates the centralinhibitory pathway. • Visceral sensory nerve activates the central inhibitory pathway On peripheral nerve: activate the motor nerve pathway	BoNT-A mainly acts on the peripheral nervous system. • BoNT-A can inhibit neurotransmitter release not only from efferent but also possibly from afferent nerve terminals. • Decline the neurotransmitter release in the presynaptic membrane. • Reduces receptors expression in the postsynaptic membrane. • Improves the sensation of the bladder by decreasing ATP in the sub-urothelium. Central effect: • BoNT-A Impairs the sensory fibers terminals in the spinal cord dorsal horn.
Compared to medications	Superior	Equal
Undesirable events	Low incidence	Higher incidence, especially UTI and urine retention
Long term stability	Long term 80% stability	Short term stability 70% of patients drop out
Satisfaction	High maintained satisfaction	Short-term satisfaction
Re-treatment	Less	Repeated in a less than a year
Cost effectiveness	Long term cost effective (5 and 10 years)	Short-term cost effective (2 years)

Table 1.
Comparison of the sacral neuromodulation and botulinum toxin treatment.

respectively. In A multicenter randomized trial that compared the 2-years outcome of BoNT-A and SNM, no difference in mean UUI episodes reduction was found (p = 0.15), with no differences in UUI resolution, ≥75% or ≥50% UUI episodes reduction [46]. Others reported that SNM had a better success rate than BoNT-A after 6 months of follow-up [47]. In a recent systematic review, no significant difference was found in successful treatment between BoNT-A and SNM at 6 months after procedures [48].

The injection of BoNT-A is associated with a significant rate of side effects, particularly urinary retention. Local discomfort and infection are prevalent in SNM and are easily managed. As a result, compared to SNM, BoNT-A injection has a safety disadvantage. Both options have opposing viewpoints on their efficacy.

The suggestion would be reconsidered if we introduced cost-effectiveness. BoNT-A injection would be a cost-effective choice over a two-year period. The results of the ROSETTA randomized trial identified that two-year costs were higher for sacral neuromodulation than for BoNT-A and persisting through 5 years [49]. While at 10 years, SNM provides a considerable possibility of symptom and quality-of-life improvement and is more cost-effective compared to BoNT-A [50]. As a result, in the long run, SNM would be the better alternative.

In the case of the non-responder who was initially treated with SNM or BoNT-A injection, we do not know whether we can switch to another therapy or how effective it will be. BoNT-A can be used in SNM non-responders with a success rate of 43.4% but is associated with a high long-term discontinuation rate (55%) [51].

Furthermore, the success rate in ROAB patients who used SNM therapy after failed BoNT-A therapy was 58.5%. There was no significant difference between ROAB patients who chose SNM as replacement therapy after failed BoNT-A therapy and those who used SNM therapy as first (**Table 1**) [52].

8. Future perspectives

As mentioned before, intra-detrusor injection of BoNT-A is still an invasive procedure that requires anesthesia and is associated with specific complications especially UTI and urine retention. Also, the efficacy and safety of intra-detrusor injection are sensitive to injection volume and depth, and this issue has motivated researchers to study injection-free modes of drug delivery into the bladder [53]. Therefore, intravesical instillation rather than injection of BoNT-A seems to be a sound idea. Nevertheless, BoNT-A delivery to the bladder tissue after intravesical instillation is hampered by toxin degradation by urine proteases, dilution by urine at the time of instillation, and poor uptake due to the urothelium impermeability, which results from the watertight barrier located at the umbrella cells in the superficial layers of bladder urothelium that are augmented by glycosaminoglycan and uroplakins [54].

To overcome this barrier, intravesical instillation of BoNT-A formulated with liposome (lipo-botulinum toxin) to enhance its absorption was evaluated in two studies; one pilot study and a 2-center, double-blind, randomized, placebo-controlled trial. After 1-month, lipo-botulinum toxin instillation was associated with a statistically significant reduced urinary frequency and urgency; however, the treatment did not reduce UUI episodes. Furthermore, onabotulinum toxin complexed with liposomes did not result in urinary retention [55, 56].

Another method tested was to add a chemical agent that enhances drug delivery into the bladder tissue. Dimethyl sulfoxide (DMSO) is an organic solvent that has been used to facilitate the delivery of several anticancer drugs into animal bladders. Petrou et al. studied 25 women with ROAB that were given BoNT-A (300 U) mixed

with 50% DMSO. Efficacy and toxicity were assessed at baseline, 1 and 3-months after treatment. The median number of UUI episodes decreased at 1 month ($p = 0.004$) and then increased back at 3 months. Also, a significant reduction in symptom scores from baseline was noted. The Impact Questionnaire short form improved from 13 to 7 at 1 month ($p = 0.007$), and the Urogenital Distress Inventory improved from 10 to 5 at 1 month ($p = 0.003$). No serious side effects or urinary retention were noted [57].

Kodama et al. stated that low energy shock waves (LESWs) increase tissue permeability and drug delivery into cells by the shear force generated by the movement of liquid relative to cells, which temporarily affects the permeability of the plasma membrane. So, it can deliver macromolecular drugs into the cell cytoplasm without toxicity [58]. In the OAB-rat model, intravesical instillation of BoNT-A plus LESW group showed statistically significant lower amplitude.

($p = 0.001$) and lower frequency of detrusor contractions ($p = 0.01$). Histologically, combined treatments significantly reduced submucosal edema and inflammatory cell infiltrate scores. Moreover, BoNT-A plus LESW significantly increased tissue expression of antioxidant marker (superoxide dismutase) and suppressed oxidative stress marker (malondialdehyde) and inflammatory cytokines (tumor necrotic factor-α and interleukin-6) [59].

In preliminary clinical study, including 15 patients with ROAB, Intravesical instillation of 100 IU of BoNT-A was done followed by LESWs (3000 shocks over 10 min) exposure to the suprapubic area was tested. Patients were followed-up by urine analysis, urine culture, PVR, and Overactive Bladder Symptom Score (OABSS) at 1, 2, and 3 months. Patients showed statistically significant improvements in all OABSS domains and the total score after 1 and 2 months of treatment ($P < 0.05$). Whereas, only the nocturia domain remained significantly improved after 3 months ($P = 0.02$). Seven (46.6%) and 12 (80%) patients were totally dry at 1 and 2 months, respectively. Also, treated patients had no significant increase in PVR throughout the study period ($P > 0.05$), and none of the patients required clean intermittent catheterization [60].

Further research to optimize the procedure of injection to be less invasive, more effective, and improve the injection-free mode is mandatory and expected in the near future.

9. Conclusion

- Intravesical injections of BoNT-A have been approved as third-line treatment for OAB after the failure of behavioral and pharmacotherapy with successful short-term outcomes.

- Repeated injections should be put into consideration during decision-making and patient counseling.

- Intravesical BoNT-A injections are associated with a significant rate of adverse events (such as increased post-void residual volume, acute urinary retention, and UTI); thus, informed consent must be given before treatment.

- No consensus on the standard injection technique and dose of BoNT-A in ROAB.

- Approaches to optimize the procedure techniques; to be less invasive, more effective, and with less side effects, improve the injection free mode and improve its outcome to be more durable are mandatory future perspectives.

Conflict of interest

Authors have no conflict of interest to disclose.

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