Botulinum toxin and urinary bladder disorders in women: new insight into an old problem

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“...and the urinary bladder; this also may be plainly observed to receive and accumulate fluid until it is so stretched by the amount of this and to be incapable of enduring the pain; or it may be the quality of urine that irritates it”.

Claudius Galen, *On the Natural Faculties*, 180–190 A.D.

The overactive bladder (OAB) and painful bladder (bladder pain syndrome/interstitial cystitis) syndromes are common urological problems that frequently co-exist and severely affect the quality of life of many women. As yet, the pathophysiology of both conditions is incompletely understood, and therefore the results of available treatment including drug therapy are usually disappointing.

Botulinum neurotoxin type A (BoNT-A) is increasingly used in humans for pharmaceutical and cosmetic purposes. The toxin is produced from fermentation of the bacterium *Clostridium botulinum*. Due to ease of administration and relatively long-lasting effects, BoNT-A is now widely used in clinical practice amongst several medical specialties, particularly in dermatology and plastic surgery mainly for cosmeceutical rejuvenation [1]. More recently, there is abundant literature supporting the use of BoNT-A in urology and urogynecology, and the off-label use of this

drug continues to grow in both disciplines worldwide. Although the first use of BoNT-A in lower urinary tract disorders was reported 22 years ago [2], evidence-based information to guide current urogynecologic practice is still lacking.

BoNT-A has unique physio-pharmacological properties that includes a muscle-paralyzing effect via inhibition of acetyl-choline release from motor nerves into the neuromuscular junction. This induces temporary chemodenervation that produces relaxation of both skeletal and smooth muscles. Another potentially very important property of BoNT-A is the ability to inhibit afferent neurotransmission inhibition. This leads to a very potent analgesic effect by inhibition of ATP secretion, reduced production of substance P, and reduced axonal expression of capsaicin, purinergic receptors, and nerve growth factors [3]. The therapeutic rationale for using BoNT-A in lower urinary tract disorders in women is primarily based on both the muscle relaxant and analgesic actions.

Anticholinergic agents are the mainstay of pharmacologic treatment of OAB because of the ability to reduce bladder contractions and associated symptoms in most patients. These drugs are, however, associated with poor tolerability and relatively poor patients' compliance because of the high incidence of anticholinergic adverse effects such as dry mouth, blurred vision, and constipation. In fact, almost 17% of participants withdrew from clinical trials of anticholinergic drugs because of this reason alone [4]. Over the past two decades, the use of cystoscopic intra-detrusor injection of BoNT-A has revolutionized the treatment of OAB, particularly the intractable symptoms associated with neurogenic OAB induced by spinal cord lesions and diseases [5]. Challenging cases of neurogenic OAB that are often associated with poor control of symptoms on standard

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anticholinergic treatment were the first group of patients who benefited from such intervention. The use of BoNT-A was effective with remarkable results [6]. There was objective improvement of all urodynamic parameters following treatment such as the maximum detrusor pressure, the detrusor compliance, and cystometric capacity. Subjective patient incontinence status also significantly improved. The improvement was observed after 2 weeks and lasted for 9 months, and the effect was maintained with repeated injections for up to 7 years thereafter. The paralyzing effect of BoNT-A on detrusor musculature, nevertheless, was not specific, occurring throughout the entire micturition cycle and affecting the normal detrusor contractions during the voiding phase as well as the overactive contractions during the storage phase. The former effect reduced the efficiency of voiding and resulted in a high incidence of clean intermittent self-catheterization after BoNT therapy [7]. This finding represented a major caveat for the wider use of BoNT-A in the treatment of non-neurogenic OAB because of the risk of urinary retention.

In a recently published *European Consensus Report* on the use of BoNT-A in the treatment of lower urinary tract disorders and pelvic floor dysfunction, 641 patients with non-neurogenic OAB refractory to oral pharmacotherapy were identified and reviewed from 29 single-injection studies [8]. The overall conclusion was that BoNT-A therapy is considered safe and is recommended for intractable symptoms associated with both neurogenic or non-neurogenic (idiopathic) OAB (Grade A recommendation). The drug should be, however, used with caution in the latter group because of the likelihood of voiding dysfunction. There are also three randomized trials comparing the efficacy and tolerance of different doses and injection techniques of BoNT-A in non-neurogenic versus neurogenic OAB patients [8]. Although these studies are not homogenous in their design, definition of response, and primary outcome or measurement of efficacy, all studies consistently showed a significant improvement in several outcomes following treatment. Efficacy rates for BoNT-A varied from 36.4% to 89% with a mean of 69%, and complete continence was achieved in 32–86% of patients with a mean of 58%. All studies also showed a significant reduction in incontinence episodes with a mean of 65%.

It is noteworthy that the effect of BoNT-A detrusor injections is not immediately observed because a significant improvement in outcome usually occurs only after the second week of injection [9]. Furthermore, the effect of BoNT-A is temporary, and therefore long-term relief of symptoms usually requires repeated injections to maintain improvement. There were some concerns regarding the potential effects of repeated injections on the integrity of the wall of the urinary bladder [10]. Patients with neurogenic OAB who were treated with BoNT-A, however,

had a lower incidence of edema and fibrosis of their bladder wall at histology than those who were not treated [11].

As yet, there is no robust data on the best dose of BoNT-A to use in patients with OAB. A dose of 300 units is most commonly used in neurogenic OAB while the dose used in the non-neurogenic population is usually lower, 150 to 200 units [8]. The technique, site, depth, or number of injections of BoNT-A are not also standardized. The original application of BoNT-A to the detrusor muscle in neurogenic patients was performed with a rigid cystoscope, but flexible cystoscopy is now becoming an alternative procedure for introducing the drug. There are no comparative studies on the number or site of injections of BoNT-A with a range from ten up to 30 injections administered in different sites of the urinary bladder. Another controversy is the necessity of sparing the trigonal area during injection. It was traditionally thought that injections in the trigone can cause or aggravate vesico-ureteral reflux because of the theoretical possibility of paralyzing the vesico-ureteral sphincter. There was no evidence, however, of new or worsening of pre-existing vesico-ureteral reflux following BoNT-A injections in the trigone [12]. Finally, it is not also clear if the neurotoxin should be injected directly into the detrusor muscle or only under the bladder mucosa.

Relief of bladder pain is an emerging potential therapeutic application of BoNT-A, with an increasing number of publications describing the use of BoNT-A for treatment of different painful conditions of the urinary bladder. Periurethral injection of BoNT-A has recently been shown to reduce post-operative bladder pain induced by a ureteral stent. In this study, 51 patients were randomized to BoNT-A (30 units around the ureteral orifice) versus no treatment, and the treated group required a significantly lower amount of narcotic analgesics in the post-operative period. There were no differences in other post-operative lower urinary tract symptoms among the two groups [13]. There are currently five open-label studies on the use of BoNT-A in patients with painful bladder syndromes. The dose of BoNT-A used for pain relief was usually lower than that used to treat OAB and ranged between 100 and 200 units [14]. Another treatment difference is the need to inject more of the drug in the trigonal area in an attempt to block the dense afferent pathways responsible for the origin of bladder pain that are mainly located in this region. The efficacy of pain relief induced by BoNT-A in patients with painful bladder syndromes varies from 20% to 79%. A limitation of most of these studies, however, is the relatively short period of follow-up that is usually 3 months. Only one study showed that the beneficial vesico-analgesic effect of BoNT-A is maintained for 5 months at 1 year follow-up [15].

At present, there is an urgent demand in the urogynecologic community for a new drug to treat women with OAB and painful bladder syndromes because the current drug

therapy is either inadequate or ineffective. Hypothetically, all smooth muscle relaxants should be helpful in treating OAB provided that their side effects at therapeutic doses are acceptable. The clinical requirement for treatment of the overactive detrusor contractions “*par excellence*” is a drug that reduces the excitability of bladder smooth muscles with no significant effects on neuronal activity or the contractility of the smooth muscle itself so as to maintain normal micturition [16]. The ability to block the painful sensory pathways that contribute to the overactivity of the detrusor muscle would be an added advantage. Although BoNT-A does not satisfy all these criteria, there is now good-quality scientific evidence to show that the drug may be an effective treatment for both neurogenic and non-neurogenic OAB. The drug also has a promising analgesic effect on the urinary bladder in painful bladder syndromes with a synergistic beneficial effect on OAB symptoms. The study of medical history, nevertheless, should remind us of the tragedies of over-enthusiasm about new pharmacological interventions in chronic medical disorders, and positive lessons must be learned. Hence, we recommend more adequately powered and long-term, randomized, controlled trials to evaluate the safety and efficacy of BoNT-A therapy in female urinary bladder disorders and to better identify women who are likely to benefit from this treatment. Until these data are available, further clinical experience with BoNT-A as a novel therapeutic agent for OAB and painful bladder syndromes in women is awaited with interest.

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