The Treatment of Overactive Bladder Syndrome Refractory to Antimuscarinic Therapy

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ABSTRACT

Overactive bladder syndrome (OAB) is a common and bothersome problem which affects about 17% of the population in western countries. The treatment of OAB is usually a challenge due to the high incidence of treatment failure and symptom recurrence. This article reviews various treatments of OAB refractory to antimuscarinic therapy. A literature search for reports on the clinical management of refractory OAB and its efficacy and safety was performed and a total of 55 articles were reviewed. Treatments included intravesical installation of vanilloid agents, intravesical botulinum toxin-A (BoNT-A) injections, neuromodulation and surgery (various types of augmentation enterocystoplasty). *Key words:* overactive bladder, vanilloid installation, Botulinum toxin, neuromodulation, augmentation enterocystoplasty

INTRODUCTION

OAB is a symptom complex associated with urgency, frequency and usually nocturia, with or without incontinence. The incidence is high especially among the aging population. It affects about 17% of the population, both men or women, in western countries [1]. First line treatments include bladder retraining, behavioral therapy, biofeedback and oral antimuscarinic agents. If refractory OAB occurs, the treatment is more complicated. Second line treatments include intravesical instillation (including anticholinergics, local anesthetics, capsaicin, resiniferatoxin), intradetrusor botulinum toxin-A (BoNT-A) injections, neuromodulation (including pudendal nerve, sacral nerve and tibial nerve stimulation) and surgery (including autoaugmentation and augmentation enterocystoplasty).

Intravesical instillation of anticholinergics or local anesthetics has a short term effect without systemic side effects [2]. However, it is not widely used and has became less popular because the lack of long-term efficacy and difficulty in catheterization in daily clinical practice. Intravesical installation of vallinoid neurotoxins (capsaicin and resiniferatoxin) requires precise preparation and the optimal dose is still controversial. Currently these treatments are still in clinical trials [3-13]. Recently, BoNT-A has emerged as a novel treatment for refractory OAB and has played an important role in the management of this disease [2,4,6,8,9,11,14-38]. In more complicated cases, neuromodulation and surgery can also provide help for refractory OAB, however definite efficacy has not been achieved with neuromodulation and augmentation enterocystoplasty is more invasive and requires a more experienced surgeon [39-54].

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INTRAVESICAL VANILLOID INSTILLATION

There are three types of receptors contributing to detrusor contraction and relaxation, the muscarinic, purinergic and adrenergic receptors. Two types of sensory innervation have been found in the bladder, the myelinated A-delta and unmyelinated C-fibers, and they are considered to be involved in the pathogenesis of OAB [5]. The latter is activated through noxious stimulation. Previously, the aim of treatment of OAB was to block the motor nervous system via the muscarinic pathway. However, recent investigations have considered OAB a sensory problem, and therefore, many clinical trials have targeted the sensory pathway through desensitization of C-fibers with acceptable treatment results [1-12].

Increased expression of the vanilloid receptors TRPV1 has been found in patients with OAB or detrusor overactivity (DO) [3-5,11]. OAB or DO refractory to antimuscarinic therapy may be due to abnormal afferent C fiber activation through these vanilloid receptors [3-5,11]. Capsaicin and rersiniferatoxin are neurotoxins that have analogue effects on the vanilloid receptors. Thus, installation of neurotoxins such as capsaicin or resiniferatoxin can deplete neurotransmitters which are released after vanilloid receptor activation, such as vasoactive intestinal polypeptides, substance P, neurokinin and nerve growth factor [13]. Further desensitizing the vanilloid pathway by blocking the receptor TRPV1 will finally cause C fiber desensitization and reduce bladder sensory input. This effect is called chemodenervation [55]. This treatment could result in a reduction of urgency perception at low concentrations and a decrease in bladder contractility at high concentrations of vanilloids. The bladder capacity can be increased and detrusor instability during bladder filling can be decreased, thus improving urinary incontinence and the quality of life [2-8,11].

De Seze et al reported 33 cases of urinary incontinence due to refractory neurogenic detrusor overactivity (NDO) treated with capsaicin (17 cases) and a placebo (16 cases). They confirmed the short term efficacy (30 days) of capsaicin in improving OAB syndrome and increasing the maximal cystometric capacity. No obvious side effects, except for transient pubic pain, were noted in the capsaicin group (58% vs 12.5%, $P<0.01$) [7]. However, capsaicin installation (1-2 mM) is associated with slight discomfort, an itch sensation and urgency. These adverse effects were not observed in instillation of another

neurotoxin, resiniferatoxin, which has a similar effect on reduction of urinary incontinence episodes in patients with OAB syndrome [2].

Resiniferatoxin binding to TRPV1 on C-fibers causes a massive inflow of calcium and other ions into the fibers, generating action potentials and releasing neuropeptides from the peripheral nerve endings [4,5]. This could cause transient reduction of bladder sensory input conveyed to the central nervous system (CNS) via the C-fibers. A recent study noted that resiniferatoxin treatment has a higher success rate in idiopathic detrusor overactivity (IDO) cases with over-expression of the urothelial and suburothelial TRPV1 receptors [3]. However, the optimal concentration of resiniferatoxin for treatment of NDO or IDO remains to be established. A lack of stable preparations of resiniferatoxin available for easy bladder installation is still problematic, and this is the reason that resiniferatoxin is not yet commercially available . Multiple installations of a low concentration of resiniferatoxin (50 to 100 10^{-9}M) might achieve a greater and more sustained response in treating patients with IDO without severe adverse effects [12]. The dosage of resiniferatoxin suggested for treatment of NDO is around 10^{-6}M to 10^{-9}M; which is higher than that used for IDO or painful bladder syndrome [12].

BOTULINUM TOXIN A (BoNT-A, BOTOX®)

BoNT was first isolated by van Ermengem in 1897. It is a potent neurotoxin produced by the gram-positive anaerobic bacterium, *Clostridium botulinum*. The toxin is a 150-kD amino acid di-chain molecule consisting of a light (50 kD) and a heavy chain (100 kD) linked by a disulfide bond [14]. BoNT was first used by Dickson & Shevky in 1923 for parasympathetic nerve blockage. Among the seven serotypes of BoNT, types A and B have been used with clinical benefits in various neurogenic disorders. BoNT-A has action on the inhibition of acetylcholine release at presynaptic neuromuscular junctions and results in striated muscle relaxation [4,14,16,20,29]. Recently, BoNT-A was also found to inhibit the release of various neurotransmitters (such as adenosine triphosphate and substance P) and thus causes the blockage of purinergic ($P2X_3$) and vanilloid receptors TRPV1 from the bladder afferent nerves and causes chemical denervation. It has been suggested that the treatment mechanism of BoNT-A occurs through blocking both the sensory and motor pathways [4,14,16].

BoNT-A was first investigated in 1990 for the treatment of detrusor external sphincter dyssynergia in spinal cord injury (SCI) patients [14]. Schurch was the first to describe the clinical effects of BoNT-A on detrusor hyperreflexia-induced reflex incontinence in paraplegia patients after intradetrusor injection [14]. Currently, the clinical applications of BoNT-A have been extended to treat patients with NDO and IDO with acceptable results [4,14,16-18,20,21,26,32,37]. Detrusor injection of BoNT-A can increase maximal bladder capacity and improve urinary incontinence and quality of life, and its effects last for more than 6 months [14]. Treatment of interstitial cystitis and painful bladder syndrome by BoNT-A injection is under investigation [4].

Some clinical trials have investigated different sites and dosages for BoNT-A injection in refractory OAB have been investigated. Kuo reported on BoNT-A (100 U) injection into the bladder body (including detrusor and suburothelial injection) and bladder base in 45 patients. The results showed that the cystometric capacity and post voiding residual significantly increased in patients undergoing detrusor and suburothelial injections into the bladder body but not in patients with bladder base injections. However, bladder base BoNT-A injection reduced the urgency sensation without increasing the risk of a large postvoid residual and acute urinary retention. The effects of BoNT-A lasted for more than 3 months [16]. A study concerning the optimal dosage of BoNT-A (100 U, 150 U and 200 U) in patients with IDO and NDO has concluded that the therapeutic effect is dose dependent in patients with NDO but not in those with IDO [24]. Different types of anesthesia can be used during BoNT-A injection, including general, spinal, intravenous sedation, and intravesical local anesthesia, and the procedure can even be done without anesthesia [21]. A rigid or flexible cystoscope can be used for bladder injection of BoNT-A [21].

In the review of the literatures, the most commonly used dosage in OAB was 300 U (dilution into 10 U/mL concentration for injection) and the lowest dose was 100 U. A high dose of 300 U BoNT-A was used in patients with NDO while a low dose of 100 U was used in patients with IDO or OAB. However, there is no consensus concerning the optimal dosage, number or location of BoNT-A injections The response rates of BoNT-A injection were around 40%-80% with complete dryness experienced between clean intermittent catheterizations. The mean maximal detrusor pressure (Pdet.Qmax) was below 40 cm H_2O and the quality of life in regard to urination was significantly improved [14]. Adverse events such as urinary tract infection, bladder pain, hematuria and autonomic dysreflexia need to be carefully managed [20]. Currently, injecting BoNT-A into the bladder is not yet approved by the US Food and Drug Administration (FDA) or the European Medicines Agency for the treatment of neurogenic detrusor overactivity (NDO) or neurogenic overactive bladder (NOAB) [14]. There are two types of BoNT-A which are commercially available, BOTOX® (Allergan, Irvine, CA, USA) and Dysport® (Ipsen-Biotech, Ireland).

NEUROMODULATION

The nervous system of the urogenital tract involves the somatic nerves (the pudendal nerve system), and the autonomic system (the sympathetic system at T_{10}-L_1 and the parasympathetic system at S_2-S_4). These three systems are regulated by the pontine micturation center. The parasympathetic system facilitates bladder contraction and completes micturition [43]. Continence is facilitated by the sympathetic (bladder relaxation and internal sphincter contraction) and pudendal nerve systems (rhabdosphincter contraction). Neuromodulation of lower urinary tract innervation can affect sensory, motor and endocrinal functions via creation of afferent and efferent nerve pulses [43]. It is an alternative treatment for patients with refractory OAB who are not yet ready for irreversible surgery. Different therapies such as pudendal nerve stimulation, sacral nerve stimulation (SNS) and tibial nerve stimulation have been developed with varying success rates.

Pudendal nerve stimulation acts on the inhibitory mode of action of the bladder to treat OAB. Bladder contractions are suppressed via the sympathetic hypogastric nerves whereas another pathway is activated via the parasympathetic pelvic nerves, resulting in central inhibition [44]. The mode of current delivery includes intravaginal or intraanal electrical stimulation and transcutaneous electrical stimulation.

SNS was approved by the FDA in the treatment of refractory voiding dysfunction in 1990, urge incontinence in 1997, and urgency-frequency syndrome and idiopathic non-obstruction urine retention in 1999 [41]. The mechanism is complex, and mainly involves modulating afferent nerves (S_3 activates the spinal inhibitory pathway) with some

modulatory effects on the somatic system and also on the sympathetic nervous system. SNS can be used in the treatment of idiopathic urinary retention for restoration of bladder perception and normal detrusor contractions and for decreasing urethral sphincter afferent activity [39,43]. Furthermore; SNS was found to modulate C fibers and thus can be used for pain control in patients with interstitial cystitis. It is suggested that SNS can induce pelvic floor muscle hypertrophy, resulting in improvement of pelvic floor efficiency [43].

Tibial nerve stimulation can decrease spinal cell activity via reducing C-fos protein expression. C-fos protein is a neuron messenger which can be activated in noxious stimulations of the bladder [43]. The tibial nerve is a mixed nerve containing sensory and motor nerve fibers. Percutaneous tibial nerve stimulation (PTNS) can modulate sacral plexus signals by retrograde afferent stimulation and thus treat refractory OAB [44]. However, the effect of PTNS is temporary and maintenance stimulation is necessary [44].

SURGERY

Cystoscopic hydrodilatation can be tried in refractory OAB but the effect is limited. Sacral nerve posterior rhizotomy has been used in SCI patients with detrusor hyperreflexia and contracture of the bladder. The excision of the posterior sacral nerve roots can destroy the afferent nerve and interrupt the bladder reflex arch, resulting in a decrease in detrusor contractions. Finally, it causes a flaccid bladder and thus decreases the intravesical pressure and increases bladder capacity [54]. If posterior sacral nerve rhizotomy is used concomitantly with anterior root electrical stimulator placement, the detrusor contraction can be restored and the patient can empty his bladder by manual electrical control [54].

Detrusor myomectomy (autoaugmentation) has been tried in some patients with bladder hypertrophy and high intravesical pressure. This operation was reported to decrease intravesical pressure in case of detrusor hyperreflexia and thus can increase bladder capacity [53]. However, perivesical fibrosis may cause treatment failure and the possibility of recurrence of a contracted bladder.

Several types of augmentation enterocystoplasty have been reported, including open enterocystoplasty and laparoscopic methods with effective results [49,51,52]. Mark et al reported a total of 23 patients with idiopathic instability (12 cases) and neurogenic hyperreflexia (10 cases) who were treated with clam enterocystoplasty, among which 12 cases were completely dry [52]. Edlund et al reported another series of 30 cases with detrusor hyperreflexia (5 cases) and IDO (25 cases) who were treated with clam surgery with a mean follow-up duration of 60 months and a 90% rate of satisfaction. No serious complications were noted [51].

Although laparoscopic augmentation enterocystoplasty is a more complicated technique, Nunez Mora et al has reported 2 patients with refractory detrusor hyperreflexia and the results showed that a low pressure bladder can be created and good continence achieved. However, this procedure needs a surgeon with great experience mainly in laparoscopic suture technique [49].

Acellular porcine dermis for bladder augmentation was tried in twelve refractory OAB cases with an average 12 months of follow-up. The results showed 10 successful cases without adverse events [50].

CONCLUSIONS

Currently, there are many therapeutic modalities available for patients with OAB refractory to antimuscarinic therapy. Intravesical installation of vanilloid agents can desensitize C-fibers and decrease sensory input, and thus reduce detrusor hyperreflexia and urinary incontinence, and increase bladder capacity by decreasing detrusor overactivity. BoNT-A, in addition to acting as a parasympathetic nerve blocker, also acts on some bladder sensory pathways and can improve the OAB symptoms. Finally, neuromudulation of the sacral nervous plexus and surgery such as enterocystoplasty can be performed by an experienced surgeon with acceptable results.

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