Clinical Application of Botulinum Toxin A in Lower Urinary Tract Dysfunction

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INTRODUCTION

Lower urinary tract dysfunction can be classified into two categories, failure to store and failure to empty. Storage failure results because of either bladder or outlet abnormalities or a combination. Abnormalities of the bladder itself mainly include involuntary bladder contractions, bladder overactivity, low compliance and increased sensation. Bladder outlet abnormalities can include intermittent or continuous decreases in outlet resistance, such as urethral hypermobility and intrinsic sphincter deficiency. Likewise, failure to empty can occur because of bladder or outlet abnormalities or a combination. Bladder side abnormalities include impaired detrusor contractility during voiding. Outlet side abnormalities include anatomic or functional obstruction and sphincter dyssynergia.

Various therapies are available to facilitate urine storage and bladder emptying. These therapies mainly consist of behavior therapy, pharmacological therapy and surgical intervention. Although conservative therapies can achieve satisfactory therapeutic results, some patients are refractory to medical treatment or cannot tolerate the side effects. In addition, surgical therapy might provide long-term successful results, but complications have been reported and some patients are afraid of invasive procedures.

THE HISTORY AND MECHANISM OF BOTULINUM TOXIN

Botulinum neurotoxin is probably the most potent biological toxin than can affect humans [1]. In 1817, Justinus Kerner in Germany first described botulinum toxin as a "sausage poison". In 1897, Emile van Ermengem identified the bacterium *Clostridium botulinum* as the producer of botulinum toxin. In 1949, Arnold Burgen's group found that botulinum toxin blocks neuromuscular transmission through decreased acetylcholine release. Botulinum toxin acts by cleaving the SNARE (soluble N-ethylmaleimide-sensitive fusion attachment protein receptor) protein, synaptosomal-associated protein-25 (SNAP-25), and inhibition of release of neurotransmitters at the presynaptic vesicle. Since 1980, onabotulinumtoxinA (BoNT-A) has been widely used in a variety of medical fields for conditions including blepharospasm, strabismus, muscle spasm, and cervical dystonia and has alos been applied in cosmetics.

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BOTULINUM TOXIN APPLICATION IN LOWER URINARY TRACT DYSFUNCTION

In urological application, Dykstra et al first described the injection of BoNT-A into the external urethral sphincter in men with spinal cord injury and detrusor-sphincter dyssynergia in 1988 [2]. Since then, many studies have investigated the effects and safety of BoNT-A in treating various lower urinary tract abnormalities. In this review, we mainly focus on the treatment results in patients with low bladder compliance, mixed urinary incontinence, urge incontinence, impaired detrusor contractility and functional bladder neck obstruction.

LOW BLADDER COMPLIANCE

Bladder compliance is defined as the change in volume relative to the corresponding change in intravesical pressure. Low bladder compliance can alter bladder wall tension, and thereby change bladder sensation and the volume threshold for micturition. In addition, lower bladder compliance is often associated with urge incontinence and upper urinary tract deterioration. Anticholinergic agents and clean intermittent catheterization are often used to treat mild to moderate poor compliance and enterocystoplasty is used for severe compliance. Recently, Horst et al reported on repeated BoNT-A injections into the bladder in 11 children (mean age 6.7 ± 5.3 years) with myelomeningocele [3]. Bladder compliance increased by 28% from 7 ± 3.5 to 9 ± 6 mL/cmH_2O. However, only one girl achieved a compliance normalized to 24 with a baseline of 12. The GKT Botulinum study group from the United Kingdom reported on repeated BoNT-A injections for idiopathic bladder overactivity in a cohort of 34 patients [4]. They not only observed significant improvements in overactive bladder symptoms and quality of life, but bladder compliance also increased from 36 to 60 mL/cmH_2O and decreases in the maximal detrusor pressure during filling were found. However, 25% patients had acute urine retention after the first injection. Thus, although BoNT-A injection into bladder is an effective alternative treatment for low bladder compliance, patients must be counselled about the possibility of intermittent self catheterization postoperatively.

MIXED URINARY INCONTINENCE AND URGE INCONTINENCE

Behavioral interventions, lifestyle modification and pharmacotherapy are the mainstays for treating overactive bladder and urge urinary incontinence. BoNT-A injected into detrusor has been successful in treating refractory urge incontinence. In 2000, Schurch et al found

that BoNT-A was effective for refractory symptoms of neurogenic detrusor overactivity [5]. In 2004, Flynn et al reported a decrease in urge urinary incontinence and improved quality of life for 3 months following injection of BoNT-A in patients with severe refractory urge urinary incontinence [6]. In 2004, Reitz et al reported promising results in 200 patients with neurogenic detrusor overactivity in Europe [7]. In 2008, Brubaker et al provided level 1 evidence that cystoscopically-guided intradetrusor injection of 200 U BoNT-A decreases urge incontinence in women with idiopathic detrusor overactivity and refractory urge incontinence. The median durability of the effect was almost 12 months. The total symptoms scores on the Urinary Distress Inventory (UDI) decreased from 110 ± 61 to 67 ± 55 ($p<0.001$). The UDI obstructive subscore did not significantly worsen but the UDI irritative subscore and stress subscore decreased significantly from 54 ± 17 to 31 ± 21 ($p<0.05$) and from 33 ± 27 to 16 ± 22 ($p<0.05$), respectively. The most interesting finding in this study was stress urinary incontinence might be improved through stabilizing bladder overactivity. This is the opposite of previous speculation that leakage of urine into the urethra can stimulate afferents and induce or increase detrusor overactivity [8]. Surgical cure of stress incontinence in women with mixed incontinence resolves urge incontinence in up to half of patients. Thus, patients with urge incontinence can benefit from treating stress urinary incontinence, and vice versa.

IMPAIRED DETRUSOR CONTRACTILITY

Impaired detrusor contractility remains a difficult problem for the urologist to treat and is usually managed with clean intermittent catheterization. The use of BoNT-A, a paralyzing agent, in the face of a "weak" bladder might seem strange and paradoxical. However, the voiding reflex can be induced by relaxation of the external sphincter. Conversely, active voluntary contraction of the urethral sphincter can cause inhibition of the voiding reflex. Based on this physiological presumption, Kuo investigated 27 patients with impaired detrusor contractility receiving transurethral injection of either 50 U or 100 U BoNT-A. Thirteen patients (48%) noted recovery of detrusor contractility and 5 patients had long-term therapeutic effects without repeated injection [9]. Ke and Kuo had a similar report in which transurethral incision of the bladder neck increased detrusor pressure significantly in 13 (59%) patients with spinal cord injury and impaired detrusor contractility preoperatively [10]. Treatment of the bladder outlet seems to reduce the inhibitor effect on detrusor contractility and restore normal detrusor function.

FUNCTIONAL BLADDER NECK OBSTRUCTION

Primary bladder neck obstruction diagnosed by videourodynamic study has been considered an important cause of lower urinary tract dysfunction in young men [11]. Alpha-adrenergic agents and transurethral incision of the bladder neck are two common treatment options. Alpha-blockers have a success rate of 54%-70% but are associated with poor long-term drug compliance. Transurethral incision of the bladder neck is curative in 82%-100%, but retrograde ejaculation might be a serious complication in young patients. In 2008, Lim and Quek from Singapore showed the short-term effects of bladder neck injection of 100 U BoNT-A in treatment of bladder neck dyssynergia in 8 young patients [12]. The International Prostate Symptom Score decreased from 19.9 to 9.9 and the maximal flow rate increased from 11.6 to 17.2 mL/sec. Recurrent symptoms were noted in 3 patients (37.5%) at 8 months. In addition, Chancellor found that BoNT-A injection to the bladder neck can also improve female bladder neck dysfunction [13]. These studies all provide promising results in the use of BoNT-A injections to treat bladder neck dysfunction.

CONCLUSION

In conclusion, the role of BoNT-A in urology has evolved exponentially and it is widely used as an adjuvant in voiding dysfunction. BoNT-A therapy represents an unlimited opportunity for adjuvant intervention and will provide physicians with increased options for addressing difficult challenges in lower urinary tract dysfunction. In the future, its utility will broaden and guide the urologist in managing various urological disorders.

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