Botulinum Toxin A Injections for Overactive Bladder

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OVERACTIVE BLADDER

Overactive bladder (OAB) is a symptom syndrome characterized by urgency frequency with or without urge incontinence that may affect the patients' quality of life [1]. OAB is diagnosed by subjective symptoms, and the core symptom is urgency. Both sensory urgency and detrusor overactivity (DO) might be involved in the pathophysiology of this symptom syndrome. This condition may wax and wane and occasionally associate with symptoms of suprapubic pain at full bladder. Current treatments are usually unsuccessful in completely eradicating the urgency sensation. Behavioral therapy or pelvic floor muscle training have been tried to relieve this bothersome syndrome [2]. Some patients with OAB and hypersensitive bladder may respond to antimuscarinic agents [3], but this treatment has some adverse effects such as dizziness, dry mouth, blurred vision, and constipation, which are intolerable to some elderly patients [4]. Intra-detrusor botulinum A toxin (BoNT-A) injection has been tried and satisfactory results have been achieved in increasing bladder capacity and decreasing the urgency sensation in patients with neurogenic or idiopathic DO [5, 6]. However, increased postvoid residual volume (PVR) or urinary retention which may develop in the first post-treatment month may prohibit its wide-spread application in patients with mild to moderate symptoms refractory to antimuscarinic agents [7].

THE UROTHELIUM AND OAB

The urinary bladder urothelium has been considered a passive barrier. However, recent evidence has demonstrated that the urothelium is a responsive structure which exhibits both sensor (ability to respond to thermal, mechanical and chemical stimuli) and transducer (ability to release chemicals) functions. Studies have also revealed that afferent nerves and urothelial cells in the bladder exhibit a number of common properties, including the expression of certain receptors and ion channels, such as transient receptor potential vanilloid receptor subtype 1 (TRPV1) [8]. In addition, localization of afferent nerves adjacent to the urothelium suggests that these cells may be targets for transmitter release from bladder nerves, or chemicals released by urothelial cells may alter afferent excitability. The alteration in afferents or urothelial cells in the pelvic viscera may contribute to the sensory abnormalities in the urinary bladder [9].

The urothelial release of neurotransmitters such as acetylcholine (ACh), adenosine triphosphate (ATP) and neuropeptides substance P, and the expression of TRPV1 and purinergic receptors $P2X_3$ strongly imply a role for the urothelium in human bladder mechanosensation [10-12]. Recent investigations also discovered a suburothelial nexus of myofibroblasts or interstitial cells that may be the substrate for a stretch-receptor organ, These cells are extensively linked by gap junctions and may respond to ATP in a mode similar to the activation of ATP-gated P2Y receptors [13,14]. The urothelial release of ACh and ATP on bladder filling has been found to increase with ageing [10] and in spinal cord neurogenic detrusor overactivity (NDO) [15], implicating an abnormal release of these neurotransmitters in the pathophysiology of DO. In the treatment of idiopathic detrusor overactivity (IDO) with intradetrusor injections of BoNT-A, a decreased immunoreactivity of $P2X_3$ expression in suburothelial fibers has been noted, which correlates with improvement in the sensation of urgency [16].

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PATHOPHYSIOLOGY OF OAB

The actual pathophysiology of OAB has not been well elucidated. Recently, the urothelium and suburothelial space have received renewed interest because of their possible role not only in mediating solute transport but also in sensing bladder fullness [17]. An abundance of suburothelial sensory nerves and ACh and ATP-containing vesicles in nerve fiber terminals have been found in the human bladder wall, suggesting the lamina propria of the bladder plays an important role in transmitting the sensation of bladder fullness and in the response of the bladder to stretch [18-20]. These stretch-sensing apparatus may transmit sensory signals as well as mediate the detrusor reflex [21]. A change in hydrostatic pressure on the apical face of the urothelium results in ATP generation, which is postulated to activate $P2X_3$ receptors on sensory nerves [22]. The $P2X_3$ receptors are co-localized with vanilloid receptor-1 and are believed to be involved in afferent pathways that control urinary bladder volume reflexes [23]. Increased stretch-activated ATP release has been reported from human urothelial cells cultured from the bladders of patients with interstitial cystitis and spinal cord injury.

In the urinary tract, nerve growth factor (NGF) is produced by bladder smooth muscle and urothelium [24]. Recent work indicates that NGF is involved in the ongoing regulation of neural function, as well as in inflammation and pain [25]. Clinical and experimental data also link increased levels of NGF in the bladder tissue and urine to painful inflammatory conditions in the lower urinary tract, such as interstitial cystitis and chronic prostatitis [26]. Bladder inflammation by intravesical irritants or in chronic interstitial cystitis leads to acute afferent nerve activity [27] and to long-term plasticity that lowers the threshold for nociceptive and mechanoceptive afferent fibers [28]. Chronic sensitization of afferent fibers might involve both peripheral and central mechanisms. Intravesical irritants cause increased expression of the c-fos protein in the lumbosacral spinal cord [29]. A rise in bladder NGF in the muscle or urothelium initiates signals that are transported along bladder afferent nerves to the dorsal root ganglion or spinal cord [30].

Recent investigations have shown that intravesical BoNT-A reduces levels of NGF in the bladder in IDO as well as NDO [31]. Although the mechanism for the reduced bladder NGF has not been elucidated, prevention of neural plasticity by blockade of NGF production has been postulated to cause reduction of urge incontinence and symptoms of DO.

It is also possible that the chronic symptomatology in bladder hypersensitivity is due to central sensitization and persisting abnormality or activation of the afferent sensory system [32]. Intradetrusor injection of BoNT-A has been found to modulate the release of neurotransmitters from sensory nerve endings, and effectively modulate the inflammatory process mediated by nociceptive afferent nerve dysfunction [33,34].

CLINICAL EXPERIENCE IN TREATING OAB USING BONT-A

BoNT-A toxin treatment of DO due to spinal cord lesion has been reported to provide satisfactory results [35,36]. Detrusor underactivity develops after detrusor injection of 300 U of Botox and lasts for 9 months. Seventy-three percent of patients with neurogenic bladder can resume a continent condition after treatment [35]. The results in achieving urinary continence and increasing bladder capacity seem promising. However, for patients with non-neurogenic DO, the therapeutic results are not as good as those in patients with spinal cord lesion [36].

Schurch et al compared detrusor injections of 200 U and 300 U Botox to a placebo in treating NDO in spinal cord injured patients. The quality of life index showed no significant difference between patients treated with 200 U and 300 U, but all treated patients showed significantly better therapeutic outcomes than those in the placebo group [37]. Grosse et al compared the intervals between repeat detrusor BoNT-A injections and found repeat Botox injections are as effective as the first one. The intervals between repeat Botox injections did not significantly differ between the first and second, the second and third, and third and fourth injection [38]. In the study of Grosse et al the improved continence volume, cystometric capacity, reflex volume and bladder compliance were significantly decreased at months 6 to 9, suggesting repeat injections are needed by this time point [38].

Sahai et al evaluated the efficacy of 200 U Botox detrusor injection for patients with IDO. The episodes of frequency, urgency and urgency incontinence were significantly reduced at week 4 and remained low by month 6. The maximal cystometric capacity increased and maximal detrusor pressure decreased, and the improvement in quality of life (indices in terms of IIQ-7 and UDI-6) also showed the same tendency at these time-points. The PVR increased significantly at week 4 but returned to baseline level by month 3. However, 33% of the patients required clean intermittent catheterization (CIC) to evacuate PVR [39].

Jeffery et al used 500 U Dysport in treating patients with IDO and found that 63% of patients became continent the first week, and 32% remained continent at 3 and 6 months. However, 35% of patients required CIC at 3 months and 22% still needed CIC at 6 months [40].

DOSAGE OF BONT-A IN OAB

Most investigators use 200 U or 300 U Botox for detrusor injections in IDO. The therapeutic results have varied greatly. Kessler et al treated 11 patients with IDO with 300 U Botox detrusor injections and the maximal bladder capacity increased from 220 to 340 mL. However, 4 patients needed CIC due to a large PVR [41]. Rajkumar et al treated 15 women with IDO with 300 U Botox detrusor injections and 14 of them had an improvement in urgency and frequency. The therapeutic effects lasted for 5-6 months [42]. Popat et al used 200 U Botox for 31 patients with IDO, and although significant improvement in bladder capacity was noted after treatment, 20% of patients needed CIC [43]. Schulte-Baukloh et al used 300 U of Botox in detrusor and urethral injections for 7 women with overactive bladder without DO. The bladder capacity increased by 20% and all patients could void without the need for CIC [44]. In this investigator's previous studies, detrusor injections of 200 U Botox provided a 73.3% success rate in 30 patients with IDO, and the mean therapeutic duration was 5.3 months [45]. However, further study using suburothelial injections of Botox at a dose of 200 U revealed excellent therapeutic results (85% success rate) can be achieved, similar to results with detrusor injections of 300 U Botox as reported in other studies [46]. In another recent study comparing 200 U, 150 U and 100 U of Botox, this investigator found that 100 U can also have an excellent therapeutic effect in IDO (73.3%) compared with the results of 200 U detrusor injections. However, there was a higher failure rate in NDO at a dose of 100 U [46].

There is no consensus about the optimal dose of BoNT-A in the treatment of refractory OAB and DO. Injection of 300 U of Botox is the most commonly used dose for NDO, whereas 200 U-300 U of Botox has been applied in treating IDO. In previous reports, the effects of 200 U of Botox on IDO were similar with suburothelial injections and detrusor injections, possibly because diffusion of the toxin occurs between the detrusor and the suburothelial space, as shown by a decrease in sensory fibers in the suburothelial space after detrusor injection of BoNT-A. However, patients receiving suburothelial injection of 200 U of Botox have a higher rate of adverse events compared to those receiving detrusor injection of the same dose [46].

Recently, the dose of Botox for IDO was further reduced to 100 U by many investigators and a satisfactory outcome could still be achieved. Werner et al treated 26 women with IDO and a 53% success rate was obtained [47]. Schmidt et al treated 100 IDO patients with an 88% success rate [48]. The therapeutic effects of 100 U Botox need further clarification. Bearing in mind that a dose-related increase of adverse events is found with increasing doses of this drug [46]. In a recent report by this author, urinary tract infection occurred in 35% of patients, a large PVR required CIC in 30%, and difficult urination was experienced in 75% [45]. This high incidence of adverse events might prohibit a second injection when lower urinary tract symptoms relapse. When the dose of suburothelial Botox was reduced to 100 U, 4.3% of patients had urinary tract infection, 30.4% had a large PVR, and 56.5% had difficult urination [46]. Therefore, adjustment of the dose of BoNT-A for IDO patients to minimize *de novo* adverse events seems mandatory.

BONT-A INJECTION TECHNIQUE FOR OAB

One important factor for a successful therapeutic outcome when using BoNT-A is adequate distribution of the toxin into the suburothelial space and detrusor muscles. Desensitization of the mechanoreceptors on suburothelial sensory fibers can result in a decrease in bladder urgency sensation and reduced sensory neuropeptide-mediated DO

[16]. Injection of BoNT-A into the detrusor muscles can cause paralysis of the affected muscle fibers [35]. Together, these effects decrease bladder sensation and increase bladder capacity. However, if BoNT-A is not adequately distributed into the bladder wall, or the toxin is injected outside the bladder wall, the desired effect might not be achieved. This fact might explain why some investigators used large doses of BoNT-A for detrusor injections but obtained therapeutic effects similar to those with suburothelial BoNT-A injections [36,41,45].

Because the bladder wall is very thin at full capacity (around 2-3 mm), it is possible that much BoNT-A solution is injected too deep and outside the bladder wall when performing detrusor injections. One MRI study showed that a percentage of BoNT-A solution diffused outside the bladder wall and BoNT-A solution was distributed to about 33% of the total bladder wall after detrusor muscle injections [49]. Inadequate distribution and diffusion of BoNT-A solution might necessitate a larger dose for effective treatment of IDO. By contrast, in suburothelial injection of BoNT-A, all of the solution is retained inside the bladder wall. In order to achieve a favorable therapeutic result, suburothelial injection of BoNT-A seems to be a better route of injection than direct injection into the detrusor muscle.

Although suburothelial injection of BoNT-A has effects on sensory fibers, detrusor contractility can also be impaired after treatment. The extent of detrusor underactivity might even be greater than with detrusor injections of BoNT-A at the same dose. For patients with DO and impaired contractility, this adverse event might cause a large PVR and urinary tract infection. To prevent these adverse events, the dose of BoNT-A and injection sites should be carefully adjusted.

SHOULD TRIGONE INJECTION BE USED ?

The trigone and bladder base have been found to have abundant sensory fibers. Injections of BoNT-A into these areas have shown therapeutic effects on idiopathic urgency frequency syndrome and interstitial cystitis [50]. Although the trigone of the urinary bladder is rich in sensory fibers, the role of trigonal sensory fibers on bladder urgency sensation and DO has not been explored yet.

The embryology of the trigone is different from the bladder body or urethral sphincter [51]. The trigone is composed of superficial and deep smooth muscles which are sensitive to small changes in pressure and may function as an early warning system of bladder filling [52]. Injection of phenol into the trigone and transvaginal denervation surgery have both been used as treatments for patients with urge incontinence [53,54]. Sensation from the trigone in these patients might be more closely related to early bladder filling rather than bladder wall stretch at capacity. Hence, treatment aimed at reducing sensation from the trigone might not improve the urgency sensation which occurs during the bladder filling phase. Moreover, paralysis of trigonal muscles resulting from BoNT-A injection might decrease the tone of muscles which control the competence of the ureterovesical junction or bladder neck.

In a recent study comparing detrusor, suburothelial and bladder base injections of 100 U Botox in 45 patients with IDO, successful results at 3 months were achieved in 14 (93%) patients with detrusor, 12 (80%) with suburothelial and 10 (67%) with bladder base injections. The success rate in the detrusor, suburothelial and bladder base injection groups decreased with time to 67%, 47% and 13% by 6 months, and 20%, 20% and 6.7% at 9 months, respectively (p=0.0253). Vesicoureteral reflux was not found in any patient after injection. Urgency severity scores improved significantly in all groups after treatment. At 3 months after treatment, significant increases in cystometric capacity and PVR compared to baseline were found in the detrusor and suburothelial but not in the bladder base group. Bladder base BoNT-A injection relieved the urgency sensation but could not increase bladder capacity [55].

Although vesicoureteral reflux might be a potential complication after BoNT-A in these areas, there has been no evidence of it so far in recent studies [55,56]. An advantage of trigonal injection of BoNT-A is that the patient is free of detrusor underactivity after treatment. Another interesting finding in trigonal BoNT-A injection is the reduction of autonomic dysreflexia in patients with NDO after enterocystoplasty. Patients with high level spinal cord injury might suffer from bladder hypersensitivity and autonomic dysreflexia when the bladder is at a small volume. Although enterocystoplasty may increase the bladder capacity, the increased sensation from the trigone might prohibit adequate distention of the augmented bladder. Trigonal BoNT-A injection can decrease sensory input from this area, reduce bladder hypersensitivity and allow the augmented bladder to improve its capacity.

CONCLUSIONS

Intravesical BoNT-A injection has been demonstrated to be effective in treating patients with OAB, and IDO as well as NDO. The bladder capacity increases, intravesical pressure decreases, and incontinence episodes decrease after BoNT-A injection. However, the high rate of increased PVR requiring CIC after treatment remains a problem. Through careful patient selection and instruction in CIC, most patients with IDO and NDO can benefit from this novel treatment.

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