Mechanism and Priority of Botulinum Neurotoxin A versus Sacral Neuromodulation for Refractory Overactive Bladder: A Review

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Abstract
Background: The treatment of common overactive bladder (OAB) has reached a consensus, but there is not a clear answer to the treatment of refractory OAB (ROAB). ROAB is defined as nonresponsive to treatment with behavioural and oral therapies. The disease can influence the physical and mental health of patients, cause poor quality of life, and create an urgent socio-economic burden. With the advancement of medical treatment, the treatment of OAB has improved significantly in the last 2 decades, especially ROAB, by the usage of botulinum neurotoxin A (BoNT-A) and sacral neuromodulation (SNM). Many studies have demonstrated their effectiveness and safety. However, which therapy is the optimal method remains unclear for patients with ROAB, and the exact mechanism involved in the procedures is still unknown. Summary: This review is to clarify the mechanisms, advantages, and disadvantages of SNM and BoNT-A in treatment of ROAB, and determine whether there is an order effect of SNM and BoNT-A in managing ROAB. Key Messages: BoNT-A and SNM mainly act on the peripheral nervous system and central nervous system, respectively. But BoNT-A and SNM may partly act on the central and peripheral nervous systems, separately. SNM may be a better choice than BoNT-A in the long time. At the same time, BoNT-A and SNM can treat the ROAB as the first and next steps, and the sequence of both would not affect the effectiveness of each other.

Introduction

Overactive bladder (OAB) is defined by the International Continence Society (ICS) as urgency with or without urge urinary incontinence but usually with urinary frequency and nocturia in the absence of urinary tract infection [1]. Many diseases can induce OAB, such as Parkinson’s disease, cerebral infarction, diabetes, and benign prostatic hyperplasia. OAB can be divided into neurogenic OAB and idiopathic OAB according to whether nerve impairment is present. OAB is highly prevalent worldwide. Irwin et al. [2] found that its overall prevalence was 11.8%, which is similar in men and women and increases with age. The prevalence of OAB in adults aged ≥18 years was 16% in men and 16.9% in women in the USA [3], and in adults aged ≥40 years, it was 15.6% for men and 17.4% for women in Europe [4]. In Asia, the prevalence of OAB was lower, but it was still 6.0% overall, 5.9% among men, and 6.0% among women according to the fifth nationwide population census of China [5]. In mainland China, the overall prevalence of OAB was 2.1%, with OAB-dry accounting for 1.0% and OAB-wet accounting for 1.1%; OAB was
more common in men than in women older than 60 years [6]. Therefore, knowing how to treat OAB and decrease its prevalence is becoming urgent.

Behavioural therapy, for example, health education, delayed urination, bladder training, fluid intake modification, reduced coffee consumption, moderate physical activity, and pelvic floor muscle retraining, is the first step for a new OAB patient. However, such modifications usually have a poor response because most patients have low compliance with outpatient service, and OAB requires a longer time to show an improvement. Next, the process comes into second-line treatment, oral drugs. Anticholinergic medication and β-adrenergic agents are common, and evidence has confirmed that they have clinical efficacy in patients with OAB [7]. However, the adverse effects of β-adrenergic agents (increased blood pressure, nasopharyngitis, urinary tract infections, and urinary retention) and anti-muscarinic agents (dry mouth, dry eyes, constipation, blurred vision, dyspepsia, urinary retention, and impaired cognitive function) limit the usage of medicines. Due to adverse effects, more than 70% of patients quit pharmacotherapy within 6 months to 3 years [8]. In addition, some patients are insensitive to oral medicine. Although different results indicate shut-off of second-line treatment, only 3.5% of patients (men and women) were treated with third-line therapy [9]. Once behavioural therapy and oral drugs are both determined to be ineffective, the patient enters the refractory OAB (ROAB) stage [10].

ROAB is defined as the failure of behavioural therapy after 8–12 weeks and the failure of at least 1 anti-muscarinic agent administered for 4–8 weeks by the 2019 AUA/SUFU guidelines [11]. The prevalence rate of ROAB is unknown but most likely represents a small portion of the total OAB population [12]. When the patients meet the ROAB diagnosis, third-line treatment is considered. Third-line treatment consists of botulinum neurotoxin A (BoNT-A) injection, sacral neuromodulation (SNM), and percutaneous tibial nerve regulation. In recent years, the effectiveness of SNM and BoNT-A has been proven, and the success rates of both are approximately 80% [13] and 60% [14], respectively. Although SNM and BoNT-A have high success rates, the mechanisms of both remain unknown. In addition, which treatment is better or more appropriate remains unclear. In this review, we will discuss what roles BoNT-A injection and SNM play and which method can be chosen preferentially.

### Botulinum Neurotoxin A Injection

#### History of BoNT-A Injection

BoNT-A, the most potent biological toxin known to humans, has a light chain and heavy chain associated with function [15]. It is used to treat strabismus, blepharospasm, muscular dystonia, hyperhidrosis, and migraine and is widely used for cosmetic purposes [16]. By the end of 1967, botulinum toxin was first shown to inhibit the bladder in rats by Carpenter [17]; in 2011, botulinum toxin was finally approved for the treatment of urinary incontinence, secondary to neurogenic detrusor overactivity [18]. Because many studies have proven its effectiveness, the US Food and Drug Administration (FDA) approved the use of botulinum toxin for the treatment of OAB in 2013 [19]. Thus, it is necessary to understand the mechanism of action.

#### Mechanism of BoNT-A

The mechanisms of BoNT-A in the treatment of OAB mainly include several parts shown in Table 1. BoNT-A can inhibit neurotransmitter release not only from efferent but also from afferent nerve terminals [14, 20]. At the same time, BoNT-A influences both the release of presynaptic neurotransmitters and the density of postsynaptic membrane receptors. In the presynaptic membrane, there is a synaptic vesicle associated protein-2 pro-
tein that binds with the heavy chain of BoNT-A and enters the presynaptic membrane [21]. Then, catabolism is processed inside the synaptic vesicles, and the 2 chains are separated, leaving the light chain as the active part [10, 13]. Next, the actual active moiety, the light chain, recognizes and cleaves synaptosome-associated protein 25, which is vital in binding vesicles to the cell membrane and prevents neurotransmitter release [17]. On the other hand, Schulte-Baukloh et al. [22] first examined postsynaptic muscular changes in receptor profiles after injection of onabotulinum toxin A. There was a significant decrease in M2, M3, P2X2, and P2X3 receptors. The receptors of M3 and M2 directly and indirectly play a key role in bladder contractility. P2X2 and P2X3, purinergic receptor proteins that may be involved in motor signalling in neurogenic OAB [18], are highly expressed in OAB patients [23, 24]. Thus, a decrease in receptors might contribute to the reduced contractility of the urinary bladder after BoNT-A injections. In addition to the abnormal motor function, excessive sensitivity of the bladder also needs to be stopped. BoNT-A works by decreasing the sensitivity of the bladder at 2 levels. A previous study proved that ATP can mediate the sensation of bladder fullness and has a role in the pathophysiology of OAB [25]. In a laboratory, neurogenic detrusor hyperactivity in rats with chronic spinal cord injury showed increased release of ATP, while NO release was reduced [26]. This suggests that disorder of these transmitters can lead to OAB and that the prevalence rate shows a positive correlation with changes in ATP. Therefore, ATP can become one of the targets to treat OAB. On the peripheral nerve, intravesicular BoNT-A injections have been shown to significantly inhibit the release of ATP from urothelial cells [13], and ATP in the suburothelial space declines, resulting in decreased bladder sensation, owing to a lack of sensory fibre activation. In the central region, BoNT-A, radiolabelled with technetium-99, was detected in the dorsal root ganglia 6 h post-injection [27], and some data revealed that BoNT-A significantly impaired sensory fibres through a mechanism involving cleavage of synaptosome-associated protein 25 at terminals in the spinal cord dorsal horn [28]. Above all, BoNT-A injections improve not only the feeling of urgency but also the behaviour of voiding.

**Sacral Neuromodulation**

**History of SNM**

SNM was developed more than one hundred years ago as a treatment for OAB. In 1988, Tanagho and Schmidt [29] first introduced an electrode implant placed in the S3–S4 sacral foramen to produce chronic electric stimulation of the sacral nerves and restore normalcy to voiding habits. After this development, many urologists proved the effectiveness of SNM, prompting the FDA approval of InterStim (Medtronic, Minneapolis, MN) for urge incontinence in 1997 and for urgency, frequency, and non-obstructive urinary retention in 1999 [30]. Subsequently, SNM achieved substantial progress and has been introduced all over the world. Now, the SNM operation has been perfected. The procedure has 2 stages, an experience period and a permanent period, to assess effectiveness before implantation of a permanent pulse generator. This process is also a minimally invasive procedure, and Bartley et al. [30] described the SNM operation in detail in their article.

**Mechanism of SNM**

SNM mainly functions in the central nervous system, differing from BoNT-A, which mainly acts on the peripheral nervous system. SNM and BoNT-A injections have emerged as third-line treatment options for patients with ROAB to initial treatment. Groen et al. [31] investigated women with idiopathic detrusor overactivity incontinence and thought SNM can suppress OAB but cannot exert the effect on urethral resistance and bladder contraction strength. However, the detailed mechanism of SNM in treating OAB is still unclear. The mechanism of SNM treatment of ROAB is shown in Table 2, which includes 2 parts of the central and peripheral nervous systems. In the matter of the central nervous system, most people...
studies conclude that afferents may play a vital role in the mechanism of SNM [32, 33]. Considering spinal cord injury, a loss of control from the brain to the bladder and activation of the spinal micturition reflex pathway lead to changes in afferent nerve activity and abnormal reflex mechanisms [34], followed by the appearance of OAB. In inflammatory disorder, C fibres play a significant role. C fibres are unresponsive in normal but activated in OAB [35]. After SNM treatment, the number of uninhibited contractions decreased, indicating that the contraction of the bladder was controlled and that OAB was alleviated [30]. Exploring the reasons, SNM may electrically stimulate somatic afferent nerves in a sacral spinal root and send signals to the central nervous system, which may restore normal bladder function [36]; in addition, activation of somatic afferent nerves inhibits bladder sensory pathways by blocking C fibres and reflex bladder hyperactivity [37]. Malaguti et al. [32] also found that SNM acts at the cortical site level by the afferent pathway, and it is specific from the sacral area to the somatosensory cortex. In addition, SNM also activates the visceral sensory nerves. This is proven by a study in which Fowler et al. [38] demonstrated that anal sphincter contraction observed during SNM is the result of an afferent-mediated response because the response is stronger with direct motor nerve stimulation. However, there are other theories that SNM can stimulate the motor nerve pathway and retrograde spinal motor neurons [33]. This is proved by a study which suggests that pelvic floor muscle contractions are due to stimulation of direct efferent during SNM testing [39].

Priority of SNM and BoNT-A

As third-line treatments for OAB, SNM and BoNT-A have extensive applications in ROAB. Currently, the data indicate that the rate of success of SNM in treating OAB is 70% [40], and 80% of patients who receive BoNT-A injection show improvement in urinary symptoms [41]. However, we still have no answer regarding which therapy is more suitable. Many factors influence the selection of procedure. BoNT-A is a simple operation that is performed under cystoscope guidance using intravenous sedation as an outpatient procedure [42], so it is minimally invasive. However, reinjection every 6 months may be needed because of its self-limited duration of effect. SNM is complex and requires a two-step surgery. This is difficult to manage and evaluate but has a longer duration compared with BoNT-A. After SNM implantation, it can last 4–6 years, or even longer. Currently, the possible injury and complexity of surgery are acceptable based on the use of more technical advances, and it is not the main consideration. Thus, a longer duration may be valued by the patients.

Beyond operation and duration, safety and effectiveness are essential aspects in selection. Usually, the efficacy and safety of BoNT-A injection and SNM are evaluated through successful treatment rates (symptoms of OAB improvement >50%) and adverse events, respectively. The efficacy and safety of BoNT-A injection and SNM to treat OAB have been evaluated in some studies [43, 44]. The studies revealed that the rate of success between BoNT-A injection and SNM was similar. However, BoNT-A injection is faced with a high rate of adverse events, particularly urinary retention. In the cohort study [45], because of the BoNT-A injection, the incidence rate of urinary retention was up to 34.9%, followed by the need for clean intermittent self-catheterization. At the same time, clean intermittent catheterization can also cause urinary infection. For SNM, local pain and infection are common and easily handled. Thus, BoNT-A injection has a disadvantage in safety compared to SNM. Moreover, there are opposite views about the efficacy of both options. The study discovered that patients implanted with SNM had a higher success rate than those who received BoNT-A injection in the short term [46]. More studies need to be carried out to assess which one has a more effective impact. Today, the first opinion is more recognizable. According to the first view, we think the SNM has a priority. However, when we introduce cost-effectiveness, the suggestion would be overturned. In a study in which the cost-effectiveness of SNM and BoNT-A injection was assessed, the authors thought that BoNT-A injection would be a cost-effective option in the first 2 years [47]. However, with the increasing duration of therapy, the cost accumulates in terms of BoNT-A injection, but that of SNM remains unchanged. Therefore, SNM may become more cost-effective. This was proven by a study [48] that deemed SNM to be cost-effective compared with BoNT-A over 10 years. Therefore, SNM would be the best option in the long term.

In addition, with regard to the non-responder who received treatment with SNM or BoNT-A injection initially, we have no conclusion whether we can choose the other therapy and how effective it will be. In recent studies, some standpoints have been proposed. Baron et al. [49] evaluated the tolerance and efficacy of BoNT-A injection after the failure of SNM for iOAB and identified that BoNT-A injection can be used in SNM non-responders.
and has a success rate of 43.4%. Moreover, a systematic review and meta-analysis suggested that patients who fail or are dissatisfied with BoNT-A can select the SNM, and the effectiveness is not significantly different [50]. It can be seen from this evidence that both SNM and BoNT-A injection can be considered the first or next step in treating ROAB, and their effects would not be influenced by each other. There are still small numbers of patients who are insensitive to both treatments; combining SNM and BoNT injection may be more effective, although further study is needed to confirm this hypothesis.

In summary, both SNM and BoNT-A injection are good choices in treating ROAB, and their mechanism still needs to be further investigated. SNM may be cost-effective in the long term and have minor side effects. With regard to the sequence of administering both, their effectiveness would not be influenced when one fails and then the other is performed. Moreover, multiple factors should be taken into consideration, especially the will of patients. Before making a decision, the patient must be informed about the operation, duration, cost, and effect of both.

Conflict of Interest Statement

There is no conflict of interest.

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