REVIEW ARTICLE

CONTENTS

The use of *Botulinum toxin* in various urological conditions

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ABSTRACT

Aim: The objective of this review paper is to comprehensively analyze and summarize the current understanding and clinical applications of *Botulinum toxin* in the field of urology.

Materials and Methods: The materials and methods for this review paper involved an extensive literature search on the use of *Botulinum toxin* in urology. Multiple online databases such as PubMed, Web of Science, and Google Scholar were utilized to gather peer-reviewed articles, clinical trials, and relevant books published within the last decades. A few articles used in the review come from before 21 century because the information is essential to fully describe the topic. Studies were selected based on their relevance to the topic, with a focus on those that reported on the clinical applications of *Botulinum toxin* in urology – we use information from other review papers, clinical trials and research papers. To expand the database, we have looked through the literature not only in English but also other languages. Thanks to this method we were able to compare the results from different countries and scientific groups all over the world. Data extracted from these sources were then analyzed and synthesized to provide a comprehensive overview of the subject matter.

Conclusions: In conclusion, *Botulinum toxin* has shown significant promise and utility in the field of urology. Its ability to effectively relax muscles has led to its application in a variety of urological conditions, including NDO, OAB, BPS/IC, DSD, BPH, CPP, and PE. The effectiveness and safety of *Botulinum toxin* have been demonstrated in numerous studies, providing a robust evidence base for its clinical use. However, further research is needed to optimize the administration methods, dosage, and treatment protocols. Additionally, more randomized controlled trials are required to establish the long-term safety and efficacy of *Botulinum toxin*, especially for conditions for which the current data is limited. Overall, *Botulinum toxin* represents a valuable tool in the urologist's armamentarium and is likely to continue to be an area of active research and development in the future.

KEY WORDS: chronic pelvic pain, *Botulinum toxin*, overactive bladder, detrusor overactivity, bladder pain syndrome

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INTRODUCTION

Botulinum toxin (*BoNT*) is a neurotoxic protein produced by the bacterium *Clostridium botulinum*. It's widely recognized for its use in cosmetic treatments, but its potent neuromodulating properties have also found numerous applications in the field of urology. By inhibiting acetylcholine release at the neuromuscular junction, *BoNT* can effectively relax muscles, making it a powerful tool in the management of various urological conditions.

AIM

The objective of this review paper is to comprehensively analyze and summarize the current understanding and clinical applications of *BoNT* in the field of urology. We aim to provide an overview of its use in various urological conditions, discuss its effectiveness, and highlight its potential future implications. The information presented in this paper is based on a thorough review of existing literature, including peer-reviewed articles, clinical trials, and relevant books.

MATERIALS AND METHODS

The materials and methods for this review paper involved an extensive literature search on the use of *BoNT* in urology. Multiple online databases such as PubMed, Web of Science, and Google Scholar were

utilized to gather peer-reviewed articles, clinical trials, and relevant books published within the last decades. A few articles used in the review come from before 21 century because the information is essential to fully describe the topic. Studies were selected based on their relevance to the topic, with a focus on those that reported on the clinical applications of *BoNT* in urology – we use information from other review papers, clinical trials and research papers. To expand the database, we have looked through the literature not only in English but also other languages. Thanks to this method we were able to compare the results from different countries and scientific groups all over the world. Data extracted from these sources were then analyzed and synthesized to provide a comprehensive overview of the subject matter.

REVIEW AND DISCUSSION

MECHANISM OF ACTION OF *BoNT*

BoNT blocks the transmission of impulses from the nerve ending to the muscle, affecting the process of the nerve ending releasing the neurotransmitter acetylcholine from the vesicles. Vesicular transport is essential for the functioning of all human cells. In the cell itself, the mechanism for delivering vesicles to the cell surface or organelles is provided by the Golgi complex, endoplasmic reticulum, and lysosomes. Directed transport is accomplished by recognition and binding by SNARE proteins embedded in membranes. For nerve cells that have numerous and functionally different contacts with other cells, the mechanism of targeted transport of intracellular vesicles is extremely important. For example, such a system is necessary for the release of a neurotransmitter and the transmission of a nerve impulse from a neuron to a muscle. The neurotransmitter is transported to the nerve ending to the presynaptic membrane, where it is stored and released when the neuron is excited by fusion of the vesicle with the presynaptic membrane. *BoNT* disrupts this binding by blocking the release of the neurotransmitter acetylcholine by motor neurons [1-3].

BoNT IN NEUROGENIC DETRUSOR OVERACTIVITY (NDO)

NDO is a urodynamic diagnosis and one of the most common manifestations of a neurogenic bladder, which may be a consequence of nerve conduction disturbances due to spinal injury, multiple sclerosis and many other neurological diseases and their consequences [4]. During a urodynamic study, pathological increases in detrusor pressure are recorded during the filling phase of the bladder, violating the basic rule of safe functioning of the bladder, namely maintaining low pressure during filling. Abnormal pressure surges or early increases can lead to impaired continence or vesicoureteral reflux, which can impair kidney function. High-amplitude contractions are especially dangerous: it is believed that a rise in detrusor pressure above 40 cmH2O clearly causes vesicoureteral reflux.

Most studies on the use of *BoNT* for neurogenic bladder dysfunction, manifested by NDO, were carried out in groups of patients with spinal cord injury and multiple sclerosis. For these patients, it is extremely important to recognize any type of NDO and take steps to eliminate it or reduce its severity. Back in 1991, a medical center in the USA studying spinal cord injuries found that, regardless of the presence of concomitant detrusor sphincter dyssynergia (DSD), NDO leads to complications in 50% of patients [5].

The effectiveness and safety of BoNT administration for NDO was studied in the DIGNITY (Double-Blind Investigation of Purified Neurotoxin Complex in Neurogenic Detrusor Overactivity) study conducted several years ago. The program consisted of 2 phase III studies. The study included patients with NDO associated with multiple sclerosis (Expanded Functional Status Scale score ≤6.5) and spinal cord injury below Th1 level. All patients had urinary incontinence due to NDO lasting more than 3 months and with 14 or more episodes of incontinence per week. The observation group included patients both receiving antimuscarinic therapy on a continuous basis and without it. All patients were able or were trained to perform clean intermittent catheterization (CIC) [6]. Patients who received BoNT therapy experienced a clinically significant improvement in quality of life compared to patients who received placebo. With repeated courses of treatment (maximum 5), the achieved values remained stable [6].

For NDO, the standard dose is 200 IU of BoNT, diluted in 30 ml of 0.9% sodium chloride solution. The drug is injected at 30 points, 1 ml of solution into each [7].

BoNT IN OVERACTIVE BLADDER (OAB)

OAB is described as a syndrome that is characterized by a feeling of urgency in relation to urination, with or without the presence of urgency-associated urge urinary incontinence (UUI). Approximately 12% to 17% of the population is impacted by this particular syndrome. Patients diagnosed with OAB who have undergone a duration of three months using one or more distinct antimuscarinic agents, frequently without sufficient therapeutic efficacy and/or incapability to withstand

the adverse reactions of the medication, are classified as refractory OAB patients [8-10]. *BoNT* injections are advocated as the established therapeutic regimen for managing refractory OAB in accordance with the guidelines outlined by the European Urology Association (EUA) and American Urology Association (AUA) [11,12].

Published studies by Nitti et al, Tincello et al, Onem et al and Mangera et al on the usage of BoNT in OAB show a significant decrease in daily frequency, urgency and incontinence episodes. There was also the improvement in the parameters measured urodynamically. The only side effect that was expressed in bigger scale compared to placebo in those articles were urinary tract infections episodes [13-16].

The EUA guidelines have demonstrated that the administration of 100 IU *BoNT* into the bladder wall surpasses the effectiveness of a placebo in relation to UUI and the enhancement of quality of life. There is no indication of reduced efficacy with repeated injections. Nevertheless, it is imperative to highlight that patients should be duly informed regarding the potential occurrence of urinary system infections and the potential need for CIC [9].

For OAB, the standard dose is 100 IU of BoNT, diluted in 10 ml of 0.9% sodium chloride solution [7].

BoNT IN BLADDER PAIN SYNDROME/ INTERSTITIAL CYSTITIS (BPS/IC)

BPS/IC can be characterized as a collection of symptoms that are distinguished by the absence of infection and other identifiable pathologies. These symptoms encompass urgency, frequent urination, discomfort in the bladder or pelvic area, as well as a sensation of pressure [17]. *BoNT* has shown promise in the treatment of BPS/IC. It has been found to have therapeutic effects in reducing bladder pain and improving urinary urgency in BPS/IC patients [18]. *BoNT* has its effect in the central nervous system and the bladder wall, with pain control and reduction of urinary urgency achieved through mast cell stabilization, modulation of TRPV (transient receptor potential cation channel subfamily V) and PGE2 pathways, and other mechanisms. Different methods of *BoNT* administration have been explored, including intravesical instillation, hyperthermia, intravesical hydrogel, and lysosomes [19]. Bladder instillation of *BoNT* in combination with electromotive drug administration has shown promising results as a novel approach for BPS/IC treatment [20]. Studies have also shown that intravesical instillations of Sapylin after *BoNT* injection can produce better clinical outcomes than *BoNT* alone in BPS/IC patients [21]. Intratrigonal injection of *BoNT* has been found to be an effective and safe long-term treatment for BPS/IC patients refractory to conservative forms of treatment.

OTHER UROLOGICAL CONDITIONS

Among other urological conditions that might be managed with *BoNT* are DSD, benign prostatic hyperplasia (BPH), chronic pelvic pain (CPP) and premature ejaculation (PE).

Studies have shown that combined injections of *BoNT* into the detrusor and external urethral sphincter muscles can reduce detrusor and urethral pressures without increasing post-void residual ratio and diaper pad use [22]. This treatment option may be beneficial for spinal cord injury patients with DSD who want to preserve spontaneous voiding [23]. Detrusor injection of *BoNT* leads to a greater improvement in autonomic dysreflexia, possibly due to decreased detrusor pressure and increased compliance [24]. However, patient satisfaction may not increase due to side effects such as exacerbated incontinence and urinary urgency.

Several studies have shown promising results in the use of *BoNT* for BPH-induced lower urinary tract symptoms (LUTS) [25,26]. *BoNT* injections into the prostate tissue have been shown to induce smooth muscle relaxation and gland atrophy, leading to a decrease in prostate volume and improvement in LUTS [27,28]. However, the optimal route of administration, effective dose, and volume of injections still need further investigation. It is also important to consider confounding factors such as placebo effect and underlying medical conditions when evaluating the efficacy of *BoNT* for BPH.

BoNT has been investigated as a potential treatment for PE. Studies have explored the use of *BoNT* in the treatment of PE, including primary PE and PE-related distress. The injection of *BoNT* into the bulbospongiosus muscle has shown promising results in improving intravaginal ejaculatory latency time and various aspects of sexual satisfaction, such as ejaculation control and sexual satisfaction scores. However, the current data on the efficacy and safety of *BoNT* in the treatment of PE are limited, and more randomized controlled trials are needed to establish its long-term safety and efficacy [29,30].

CONCLUSIONS

In conclusion, *BoNT* has shown significant promise and utility in the field of urology. Its ability to effectively relax muscles has led to its application in a variety of urological conditions, including NDO, OAB, BPS/IC, DSD, BPH, CPP, and PE. The effectiveness and safety of *BoNT* have been demonstrated in numerous stud-

ies, providing a robust evidence base for its clinical use. However, further research is needed to optimize the administration methods, dosage, and treatment protocols. Additionally, more randomized controlled trials are required to establish the long-term safety and efficacy of *BoNT,* especially for conditions for which the current data is limited. Overall, *BoNT* represents a valuable tool in the urologist's armamentarium and is likely to continue to be an area of active research and development in the future.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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