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Review Article

Onabotulinumtoin-A for the treatment of interstitial cystitis refractory to conventional therapy

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ABSTRACT

Botulinum toxins (BoNTs) are well known for their ability to potently reduce noxious inputs by decreasing neuropeptide release, including glutamate, calcitonin gene-related peptides, and substance P from the central endings of bladder sensory nerves. Bladder pain is associated with interstitial cystitis (IC) and painful bladder syndrome (PBS), which is frequently excruciating and intractable. The use of onabotulinumtoxin A (BoNT-A) to relieve this type of bladder pain has not been well described. This article reviews the procedures and efficacy of intravesical onabotulinumtoxin-A injection as a treatment for IC/PBS that is refractory to conventional therapy.

1. Introduction

According to the definition of International Continence Society [1], the syndrome of intersittial cystitis (IC)/painful bladder syndrome (PBS) is characterized chronic bladder pain, which is aggravated by bladder distension, urinary frequency, and urgency during daytime or nighttime. The European Society for the Study of Interstitial Cystitis (ESSIC) suggests that the diagnosis should be based on chronic pelvic pain of more than six months that is accompanied by at least one other urinary symptom such as persistent urgency or frequency in the absence of active urinary tract infection and other pathology [2]. IC/PBS usually results in severe pain and this impairs the quality of life of these patients. However, current treatments are usually unsuccessful and do not either completely eradicate bladder pain or increase significantly bladder capacity [3].

The pathophysiology of IC/PBS is not fully understood. It is known that the suburothelial space of urinary bladder is well supplied with sensory nerves, which transmit the normal and noxious sensation of bladder fullness and bladder inflammation, respectively [4,5]. The possible pathomechanism of IC/PBS is that repeated insults, such as urinary tract infections or chemical irritations to the bladder, excite sensory nerves that are located in the bladder wall. These repeated or chronic excitations seem to result in an inflammatory response or neurogenic inflammation, which induces the release of the neuropeptide substance P. This causes the release of mast cell mediators, histamines, cytokines, cell and tissue damage, and finally fibrosis. These conditions result in the development in the nervous system of neuroplasticity via c–fibers that produce bladder pain [6]. Onabotulinumtoxin A (BoNT-A) affects bladder pain by decreasing the release of glutamate, calcitonin gene-related peptides and substance P from the central endings of bladder sensory nerves [7]. As a consequence, neurogenic inflammation is reduced, and nociceptive transmission to the spinal cord is inhibited. Animal studies have demonstrated that a detrusor injection of BoNT-A has the effect of increasing bladder capacity and compliance [8]. Inhibition of the neuroplasticity of the sensory fibers in the suburothelial space by intravesical BoNT-A injections seems to have the potential to treat bladder pain and sensory urgency in patients with IC/PBS [9]. Several investigators have evaluated the efficacy of different BoNT-A injections for the treatment of IC/PBS and the results have been positive in selected patients. In this review, we introduce the injection technique, explore the follow-up protocols and review the literature.

2. Injection techniques and follow-up

A total of 100 units of BoNT-A (Allergan, Irvine, CA, USA) diluted in 10–30 mL of preservative saline (i.e., 10 units/mL, 1 mL/injection)

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are injected submucosally throughout the bladder using an endoscopic injection needle followed by cystoscopic hydrodistention under intravenous general anesthesia. Our method is to inject at 40 sites within the suburothelial layers. The injection needle is inserted into the urothelium via the posterior and lateral walls of the bladder using a 23-gauge needle and rigid cystoscopic injection instrument (22 Fr, Richard Wolf, Knittlingen, Germany). Cystoscopic hydrodistention is performed to an intravesical pressure of 80 cm water for 15 minutes and the maximal bladder capacity (MBC) under hydrodistention is recorded. After the procedure, a 14 Fr urethral Foley catheter remains in place for 1 day and the patient is discharged on the next day. Oral antibiotics are prescribed for 7 days.

3. Urodynamic study

Videourodynamic studies were performed using standard procedures involving a 6 Fr dual channel catheter and an 8 Fr rectal balloon catheter. Cystometric studies were performed with warmed normal saline at a filling rate of 20 mL/minute. All descriptions and terminology in this report are in accordance with the recommendations of the International Continence Society [1]. After the videourodynamic study, 40 mL KCl solution of 0.4 M is infused slowly into the bladder and the test is regarded as positive when a painful (a Visual Analogue Score (VAS) score of two or more) or an urgency sensation is elicited compared with normal saline infusion during the prior urodynamic study [10,11].

4. Clinical assessment

Patients were requested to record a 3-day voiding diary prior to treatment in order to obtain the bladder capacity, urinary frequency and the episodes of nocturia. The IC/PBS symptoms were assessed by the O'Leary-Sant symptom index (ICSI) and problem index (ICPI) [12]. The pain score was reported by self-assessment using a 10-point VAS system. The videourodynamic study and potassium chloride (KCl) sensitivity test were then performed and the patients were informed of the possible complications associated with BoNT-A injection, such as generalized muscle weakness, difficult urination, transient urinary retention, or urinary tract infection. Outcome measures were the change in the sum of the ICSI and ICPI [12] and the change in the VAS score from baseline to 6 months after the BoNT-A injection.

Treatment outcome was also assessed using the global response assessment (GRA). Patients were requested to rate their bladder symptoms compared with baseline on a seven-point centered scale from markedly (−3), moderately (−2) and slightly worse (−1), no change (0), to slightly (+1), moderately (+2), and markedly improved (+3). Patients with moderately and markedly improved results after treatment were considered to have a successful treatment outcome. Otherwise, the treatment was considered to have failed.

5. Efficacy

Our studies demonstrated that intravesical injection of BoNT-A significantly improved patients' symptoms especially for the items bladder pain, urinary symptoms and quality of life. Based on our results, the injection of BoNT-A with cystoscopic hydrodistension also significantly reduced the urinary concentration of nerve growth factor. In addition, Nerve growth factor (NGF) mRNA production in bladder tissue has been found to be significantly increased in patients with IC compared with controls and successful intravesical BoNT-A injection was found to reduce NGF mRNA expression back to normal levels [13]. It is well known that NGF is one of the most essential neurotrophic transmitters for the growth and maintenance of multiple nociceptors. It would be expected that a reduction in the level of NGF present in the urine is likely to also contribute to a decrease in bladder pain. Pinto et al also found that urinary NGF reduced after BoNT-A trigonal injection [14]. On the other hand, they identified that brain-derived neurotrophic factor (BDNF), another ubiquitous neurothrophin with nociceptive activity [15], is also decreased on BoNTA treatment. In the literature, one pilot study by Giannantoni [16] showed that injection of 200 U of BoNTA in 20 sites reduced bladder pain in 73% of the patients at 5 months. Smith and colleagues [17] injected 100 U or 200 U BoNT-A submucosally in 13 patients, among whom near 70% patients experienced improvements in clinical symptoms with a therapeutic duration of 9 months. In our 6 months of follow-up involving 67 patients who were refractory to conventional therapy, we demonstrated that there was a significant decrease in bladder pain scores at 3 and 6 months after intravesical BoNT-A injections [18]. The incidence of serious adverse events associated with this therapy was limited and reversible. In addition, our results demonstrated the BoNT-A has a clinical effect in terms of reducing bladder pain, increasing functional bladder capacity, and improving the patient's quality of life. The only randomized controlled study reported by Gottsch and colleagues [19] failed to demonstrate the efficacy of BoNT-A injection for IC/PBS. However, their injection method was periurethrally and the dose was smaller at only 50 U [19]. Recently, a meta-analysis performed by Giannantoni and colleagues [16] also evaluated eligible randomized and nonrandomized control trials and the results revealed a great heterogeneity in methodology, questionnaires, treatment protocols, and follow-up modalities. This heterogeneity is attributable to a lack of a full understanding of the physiopathology [20]. Taken together, in the future, we believed the optimal urological care for patients with IC/PBS should be established via a well-designed randomized trial with large patient numbers, a well-defined and accepted protocol and reasonable outcome assessment tools.

6. Perspective

Currently, the optimal injection technique, including dose, dilution, and number of injections and location of injections for IC/BPS, is not standardized. Further randomized clinical trials that enroll large numbers of patients are mandatory to validate the benefit of this specific procedure and to establish standard injection sites, a standardized dose and an appropriate technique.

7. Conclusions

Treatment involving intravesical injections of BoNT-A in selected patients with refractory IC/BPS, who have failed to respond to conventional therapy, is able to reduce bladder pain, minimize urinary symptoms and improve the patient's quality of life. However, randomized trials that are methodologically sound and have sufficient power because of large patient numbers as well as an appropriate follow-up period are not available at present. Such trials are needed and, in addition, the study design should include an approach that assesses the optimum dose of BoNT-A as well as the best sites for injection.

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