Review Article

Onabotulinumtoxin-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 interstitial 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)
are injected submucosally throughout the bladder using an endo-
scopic 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 inser-
ted 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). Cysto-
scopic 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 associ-
ated 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 hydro-
distention 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 neuro-
rophic factor (BDNF), another ubiquitous neurotrophin 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 Gian-
nantoni and colleagues [16] also evaluated eligible randomized and
nonrandomized control trials and the results revealed a great
heterogeneity in methodology, questionnaires, treatment proto-
cols, 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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