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Review Article

The clinical application of intravesical botulinum toxin A injection in patients with overactive bladder and interstitial cystitis

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Abstract

Botulinum toxin A (BoNT-A) has been widely used in several urological functional disorders including neurogenic detrusor overactivity (NDO), overactive bladder (OAB), lower urinary tract dysfunction, and interstitial cystitis/bladder pain syndrome (IC/BPS). Chronic inflammation is found in a large proportion of patients with OAB and IC/BPS. The chronic inflammation activates sensory afferents which resulting in central sensitization and bladder storage symptoms. Because BoNT-A can inhibit the sensory peptides released from the vesicles in sensory nerve terminals, the inflammation can be reduced and symptom subsided. Previous studies have demonstrated that the quality of life improved after BoNT-A injections, both in neurogenic and non-NDO. Although the use of BoNT-A in treatment of IC/BPS has not been approved by FDA, intravesical BoNT-A injection has been included in the AUA guideline as the fourth line therapy. Generally, intravesical injections of BoNT-A are well tolerated, though transient hematuria and urinary tract infection can occur after the procedure. In order to prevent these adverse events, experimental trials have been conducted to test if BoNT-A can be delivered into the bladder wall without intravesical injection under anesthesia such as using liposomes encapsulated BoNT-A or application of low energy shock wave on the bladder to facilitate BoNT-A penetrating across the urothelium and treat OAB or IC/BPS. This article reviews current clinical and basic researches of BoNT-A on OAB and IC/BPS.

Keywords: *Botulinum toxin, Interstitial cystitis, Overactive bladder*

Introduction

The clinical applications of botulinum toxin A (BoNT-A) in Urology included (1) neurogenic detrusor overactivity (NDO), (2) refractory idiopathic overactive bladder (OAB), (3) interstitial cystitis/bladder pain syndrome (IC/BPS), (4) lower urinary tract symptoms due to benign prostatic hyperplasia or primary bladder neck obstruction, (5) chronic pelvic pain syndrome, and (6) neurogenic or nonneurogenic lower urinary tract dysfunction in children. This review article will focus on the applications in OAB and IC/BPS.

Pathophysiology of urothelial dysfunction in overactive bladder and interstitial cystitis/bladder pain syndrome

The bladder epithelium, known as urothelium, provides passive barrier to prevent absorption of urine and its content. Recent evidence suggests the urothelium might be a responsive organ with sensory and transducer functions [1]. Bladder sensation can be transmitted by the myelinated A-δ nerves and unmyelinated C-fibers. Many C-fibers in the bladder urothelium contain sensory neuropeptides which can modulate the micturition reflex and cause detrusor overactivity (DO) [2].

Chronic inflammation is found in a large proportion of patients with OAB and IC/BPS [3]. Chronic inflammation leads to increase of urothelial cell apoptosis, lower adhesive protein E-cadherin, and lower tight junction protein zonula occludens-1 expression [4]. The chronic inflammation in the IC/BPS bladders also inhibits the basal cell proliferation, causing defective apical cell maturation and impaired barrier function [5]. In order to abolish the inflammation and restore

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normal sensory and motor function, BoNT-A has been used to treat OAB and IC/BPS [6].

Mechanism of botulinum toxin A on overactive bladder and interstitial cystitis/bladder pain syndrome

The action of BoNT-A is initiated by the heavy chain of BoNT-A binding to the SV2 on the neuronal surface and internalization of toxin in the nerve terminal [7]. The light chain of BoNT-A cleaves synaptosome-associated protein 25 (SNAP-25) and inhibits signal transmission by disrupting the fusion of neurotransmitter-containing vesicles. BoNT-A also alters the release of adenosine triphosphate (ATP), neurotrophins, and nitric oxide (NO) in the urothelium. In patients who responded to BoNT-A injection or liposome encapsulated BoNT-A (lipotoxin) instillation, immunohistochemistry staining showed the presence of cleaved SNAP-25 and decrease of purinergic receptors P2 ×3 in the bladder urothelium [8-10].

After BoNT-A injection in patients with OAB and IC/BPS, previous studies have shown effective improvement of bladder storage symptoms with reduction of urinary nerve growth factor (NGF) levels [11-13]. BoNT-A can inhibit COX-2 and EP4 expressions in the bladder tissue and block inflammation and overactivity [14]. Moreover, BoNT-A has a neuromodulatory or anti-inflammatory effect, resulting in long-term sensory effect, possibly through central nervous system desensitization [15].

After BoNT-A injection, the release of acetylcholine from parasympathetic nerves is blocked [9,16]. In humans with NDO, the bladder muscarinic receptors M2 and M3 and purinergic receptors P2X2 and P2X3 are reduced after detrusor BoNT-A injections. The BoNT-A effect on inhibiting DO is acting through the inhibition of both the sensory and motor arms of the micturition reflex [17]. Therefore, the bladder capacity increases and voiding pressure decreases after BoNT-A injection. The bladder wall is very thin, if the injecting needle is inserted too deep, BoNT-A could be injected outside the bladder wall. Therefore, suburothelial BoNT-A injection might be a better administrating route to deliver BoNT-A into the bladder wall, and ensure all the BoNT-A solution can be kept in the bladder wall [18].

Therapeutic effects of botulinum toxin A on overactive bladder

OAB is often managed from behavioral therapy and oral pharmacotherapy, if failed, the refractory OAB will be treated with 3rd line or 4th line invasive therapy [19,20]. Currently, about 70% of OAB can be adequately treated by combined oral medications such as antimuscarinics plus mirabegron [21]. For refractory OAB, we should consider systemic etiology, neurogenic factors, or bladder outlet obstruction at the bladder neck. A video urodynamic study can find out occult bladder outlet obstruction in OAB patients with small prostate and refractory to medical treatment [Figure 1]. Patients might also have a tight bladder neck and urethral sphincter and bladder diverticulum [22].

Previous studies have demonstrated that the quality of life improved after BoNT-A injections, both in neurogenic and nonneurogenic DO [23]. However, therapeutic effect would decrease gradually with time, at 6–9 months after the prior treatment, repeat BoNT-A injection is necessary to maintain the therapeutic efficacy [24]. BoNT-A injection can also reduce bladder urgency frequency sensation. Intravesical injection of BoNT-A can effectively block ATP as well as acetylcholine (Ach) release, which is postulated to ameliorate acute pain and urgency sensation [25]. BoNT-A significantly inhibits the release of ATP and neurotrophins from urothelial cells and increased release of NO [9,10]. Reduction of urgency severity is associated with long-term therapeutic effect after intravesical BoNT-A injection for OAB [15]. OAB patients with a greater improvement in urgency severity score are associated with a higher global assessment response after BoNT-A injection, indicating the importance of sensory effect on the treatment outcome of OAB [15].

For OAB treatment, BoNT-A can be injected in different option: (1) injecting in the suburothelium or detrusor muscle at twenty sites of bladder body, with or without including trigone; (2) injecting at forty sites to cover the whole bladder wall, or (3) injecting at the trigone alone [25] [Figure 2]. Injecting at trigone has similar therapeutic effect as bladder body but carries a less risk of large postvoid residual (PVR) volume and acute urinary retention (AUR) [26]. However, the therapeutic effect of BoNT-A injection at bladder base (the area above interureteric ridge) is a little inferior to that of bladder body injection [27]. After several clinical trials and double-blind, dose-ranging trials, the results suggested that 100 U BoNT-A is the dose that has best balanced benefits with safety in general OAB patients [28].

Several phase 3 clinical trials of BoNT-A on OAB patients confirm the safety and efficacy of this treatment, and 100 U BoNT-A is the optimal dose for OAB. An European randomized, double-blind, placebo-controlled trial revealed that BoNT-A 100 U was well tolerated and demonstrated significant and clinically relevant improvements in all OAB symptoms, patient-reported benefit, and health-related quality of life in patients inadequately managed by anticholinergics [29]. The EMBARK Study Group demonstrated BoNT-A 100 U showed significant, clinically relevant improvement in all OAB symptoms and health-related quality of life in patients inadequately treated with anticholinergics and was well tolerated [30]. Herschorn *et al*. also showed that BoNT-A had significantly greater decreases in urinary incontinence than solifenacin with a third of patients achieving a 100% incontinence reduction [31]. Long-term BoNT-A treatment consistently decreased OAB symptoms and improved quality of life with no new safety signals [32].

In OAB patients with urinary incontinence, BoNT-A 100U demonstrated significant improvements across the individual domains of the quality of life questionnaires, regardless of clean intermittent catheterization [CIC]) or urinary tract

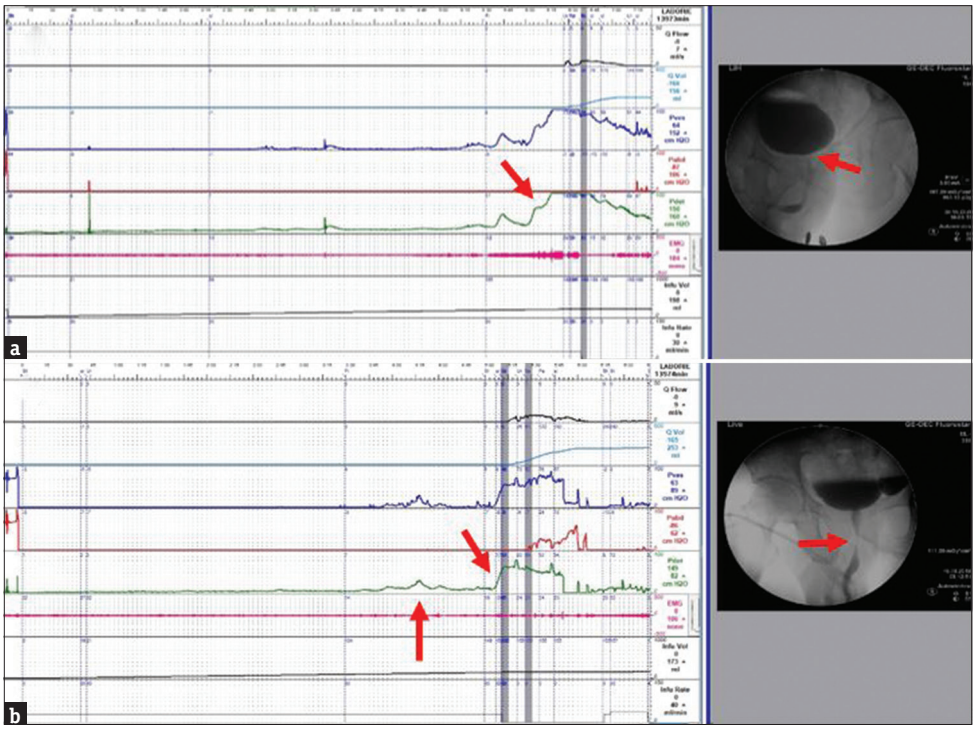

Figure 1: Video urodynamic study of male patients with overactive bladder refractory to medical treatment. (a) Terminal detrusor overactivity and primary bladder neck obstruction (arrows), and (b) phasic and terminal detrusor overactivity and dysfunctional voiding (arrows)

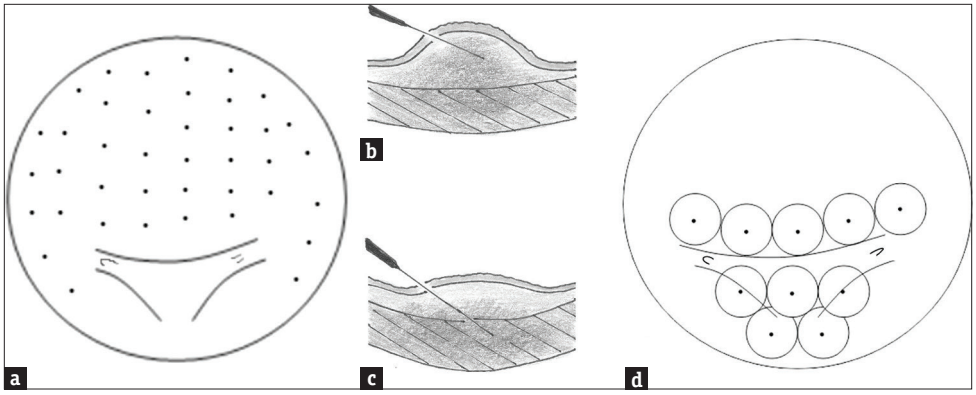

Figure 2: Intravesical botulinum toxin A injection. (a) Botulinum toxin A can be injected at 40 sites, (b) in the suburothelium or (c) detrusor muscle of the bladder body without including trigone, or (d) injecting at 10 sites at the bladder base and trigone

infection (UTI) status and provided a positive impact on practical aspects of patients' daily lives [33]. However, the efficacy of intravesical BoNT-A injection for detrusor hyperactivity and impaired contractility (DHIC) patients was limited and short term [34]. Nevertheless, the adverse events do not increase in DHIC after BoNT-A injection. Intravesical BoNT-A might not be a good indication in patients with DHIC and high PVR volume. Physicians should inform patients of the potential benefits and risks of BoNT-A injection for treatment of DHIC.

Repeated BoNT-A injections for refractory OAB are safe and effective. The most common reasons for discontinuing medication were poor efficacy and CIC-related issues [35]. However, large PVR volume and dysuria after BoNT-A injection remain the most bothersome adverse events in OAB patients. The maximum effects occur at 1–2 months; then the voiding efficiency (defined by the percentage of voided volume in total bladder capacity) will gradually return [36]. Patients planned for BoNT-A injection should be informed about this possible treatment result in advance [36]. In case, patients had PVR larger than 200 mL, CIC might be necessary to avoid subsequent UTI. Frail elderly patients are more vulnerable to experiencing complications. Around 60% of the frail elderly patients had PVR >150 mL and 11% of the patients had AUR after BoNT-A treatment. Catheter indwelling or CIC may be needed more frequently in the frail elderly after BoNT-A injection for OAB. We also observed that the cumulative success rate was significantly lower in the frail OAB elderly [37].

Therapeutic effects of botulinum toxin A on interstitial cystitis/bladder pain syndrome

Although the use of BoNT-A in treatment of IC/BPS has not been approved by FDA, intravesical BoNT-A injection has been included in the AUA guideline as the 4th line therapy [38]. Intradetrusor BoNT-A may be administered if other treatments fail to provide adequate symptom control and quality of life improvement. However, patients must be willing to accept the possible consequence that CIC is necessary after BoNT-A treatment [38]. After BoNT-A injection, bladder pain reduction and functional and cystoscopic bladder capacities increased are noted. Pain, frequency episodes, and symptom scores improved and the effects remained in more than 50% of patients for 9 months. Significantly, better success rate was achieved in IC/BPS patients who received repeated injections of 100 U BoNT-A for 3–4 times every 6 months than that in patients treated with single BoNT-A injection [39-41].

In the pathophysiology studies, BoNT-A can block the transient receptor potential vanilloid receptor subtype 1 (TRPV1) trafficking to the membrane during bladder inflammation and inhibit the inflammatory sensitization of TRPV1 [42]. Intravesical BoNT-A injections could reduce both urinary NGF and brain-derived neurotrophins levels in IC/BPS patients and render an analgesic effect [11]. BoNT-A administration to the rat bladder can also decrease the amount of spinal cord C-fos protein expression due to chronic bladder inflammation, suggesting BoNT-A can have an anti-inflammatory effect [43,44].

The urothelium of patients with IC/BPS might be in a status of persistent or chronic inflammation and injury that may relate to the limited expression of cell proliferation proteins [45]. In electron microscopic findings, significant urothelial defects in the umbrella cells were noted, defects of umbrella cells may play an important role in the pathogenesis of IC/BPS [46] [Figure 3]. Previous animal and human bladder studies have shown that BoNT-A injection can reduce the expressions of P2X3, CGRP, TRPV1 from the sensory nerves, indicating BoNT-A can inhibit the releases of these neuropeptides mediating pain and urgency sensation [47,48].

Early clinical study demonstrated BoNT-A injection plus hydrodistention can reduce bladder pain and improve IC symptoms. NGF mRNA levels were reduced in the responders versus nonresponders and in patients with reduced versus nonreduced pain visual analog scale, after BoNT-A injection [11]. Our previous study had demonstrated that the dose of 100 U BoNT-A is adequate to achieve symptomatic improvement. Although 200 U BoNT-A seems to be more effective, the adverse effect of difficulty in urination and urine retention might be a problem to be solved [39]. Based on this study, we prefer to treat IC/BPS with 100 U BoNT-A.

After BoNT-A treatment, the apoptotic cells and the activation of mast cells decreased after repeat BoNT-A injections [6] [Figure 4]. The proliferative markers Ki-67 and adhesive protein E-cadherin increased after repeated intravesical BoNT-A injections [6]. The apoptotic markers Bax and p-p38 expressions were downregulated in the patients who underwent three repeated intravesical BoNT-A injections and had symptomatic improvement [6]. Under cystoscopic hydrodistention, improvement of MBC, and glomerulations grade are noted after repeated intravesical BoNT-A injections [49].

The cumulative success rates of the patients receiving single injection or different numbers of repeated BoNT-A injections revealed that patients who received 3 or 4 repeat BoNT-A injections had better success rate than single injection [41] [Figure 5]. However, we found the BoNT-A effect on Hunner's IC is limited. Several clinical trials confirmed the efficacy and safety of BoNT-A injection in IC/BPS. A prospective, multicenter, randomized, double-blind, placebo-controlled clinical trial revealed 100 U of BoNT-A effectively reduced bladder pain symptoms in patients with IC/BPS, with acceptable adverse events [50]. Pinto *et al*. also showed that BoNT-A 100 U caused significant and clinically relevant improvements in bladder pain and quality of life in patients with IC/BPS refractory to common therapy, and the treatment was well tolerated [51]. A recent systematic review with meta-analysis revealed BoNT-A intravesical injections significantly improve some of the most relevant symptoms affecting IC/BPS patients [52].

Adverse effects of botulinum toxin A on overactive bladder and interstitial cystitis/bladder pain syndrome

Regarding the adverse effects of BoNT-A on OAB and IC/BPS, the dose-dependent occurrence of UTI is the most bothersome adverse events [53], with occasional report of *de novo* urinary retention [54]. Autonomic dysreflexia after BoNT-A injection might occur in neurogenic DO due to spinal cord injury but rarely in patients with OAB or IC/BPS [55]. The risk factors for increasing adverse events after BoNT-A injection for DO include male gender,

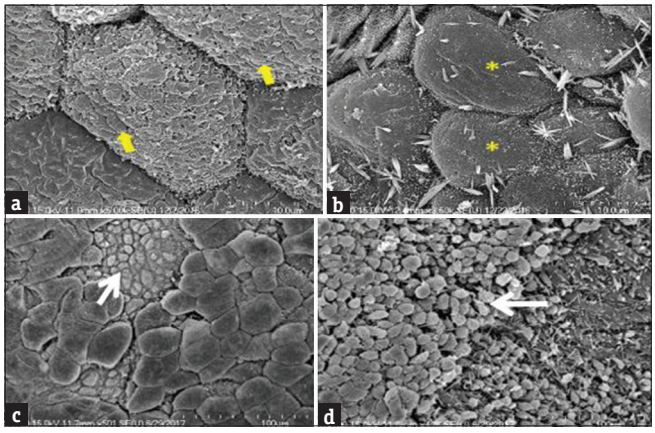

Figure 3: Electron microscopic findings in interstitial cystitis/bladder pain syndrome bladder revealed significant urothelial defects in the umbrella cells were noted. (a and b) Large hexagon apical cells (arrows and asterisks) in the normal bladder urothelium. (c and d) The small intermediate cells (arrows) were remarkable between the defects of the urothelium, resulting in bladder irritation during bladder filing

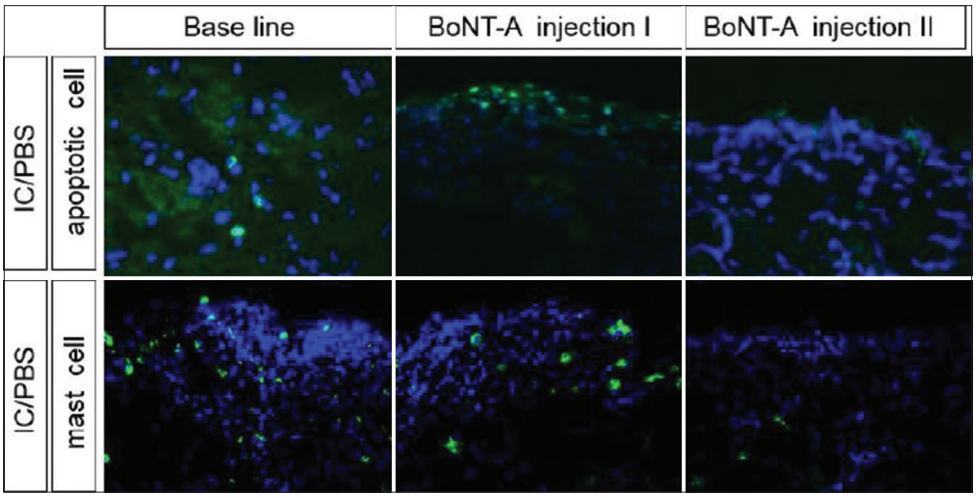

Figure 4: The interstitial cystitis/bladder pain syndrome bladders show increase of apoptotic cells and mast cells at baseline. After repeat botulinum toxin A injections, the apoptotic cells and the activation of mast cells decreased

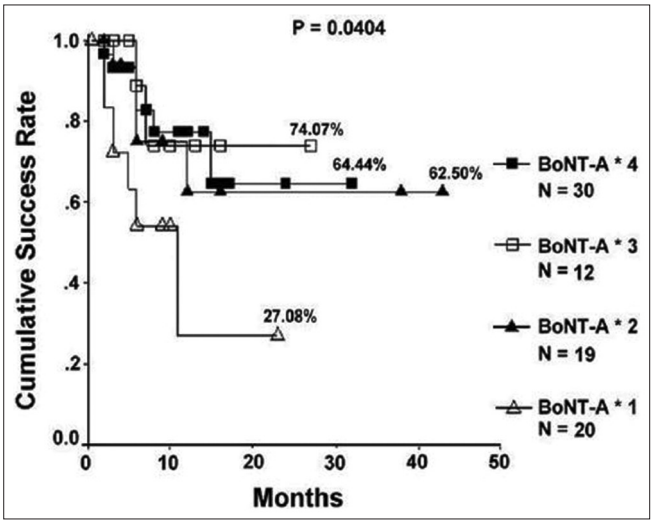

Figure 5: The cumulative success rates of the interstitial cystitis/bladder pain syndrome patients receiving different numbers of botulinum toxin A injections revealed that 3 or 4 botulinum toxin A injections provided better success rate than single injection

baseline PVR volume ≥100 mL, comorbidity, and BoNT-A dose >100 U [36]. Interestingly, these adverse events are more frequently occurred in OAB than IC/BPS patients. Elderly patients with OAB may have an increased risk of large PVR volume and a lower long-term success rate after BoNT-A injection [37]. Generally, intravesical injections of BoNT-A are well tolerated, though transient hematuria and UTI can occur after the procedure. Systemic reactions after local injections are rarely reported. Generalized paralysis has never been reported. Nevertheless, there are some reports describing a transient, mild muscular weakness in the upper limbs after BoNT-A injection [56].

Future perspectives of botulinum toxin A therapy of overactive bladder and interstitial cystitis/bladder pain syndrome

In order to prevent these adverse events, experimental trials have been conducted to test if BoNT-A protein can be delivered into the bladder wall without injection under anesthesia. Animal study demonstrated liposomes have the ability to carry BoNT-A molecules across the urothelial barrier [57]. A pilot multicenter trial confirmed intravesical instillation of mixed 80 mg liposomes and 200 U BoNT-A significantly decreased daily frequency and urgency episodes in patients with OAB, without an increase in PVR or risk of UTI. Only 50% of OAB patients responded to treatment and the effect on urgency urinary incontinence was limited in short-term follow-up [58].

Our recent study also showed BoNT-A instillation plus low energy show wave therapy applied on the bladder of IC/BPS patients could decrease bladder pain symptom [59]. Immunohistochemistry staining demonstrated the presence of cleaved SNAP-25 in the bladder mucosa, indicating BoNT-A molecules could penetrate across the urothelium after low energy shock wave applications on the bladder [60]. If the treatment is effective, this administration might replace the BoNT-A injection to treat OAB or IC/BPS.

Conclusions

BoNT-A suppresses DO and modulates sensory function, inflammation, and glandular function. Patients may experience less urgency and urinary incontinence, which are associated with a better quality of life. Adverse events such as large PVR, AUR, and UTI are common, patients must be well informed before treatment. In frail patients and DHIC, BoNT-A injection should be performed carefully to prevent AUR and subsequent UTI. Clinical trials of BoNT-A for IC/BPS have shown promising therapeutic effects in reducing bladder pain. Decrease of inflammation and apoptosis, improvement of barrier protein, and proliferation protein expressions were noted after BoNT-A treatment. Patients might have symptom relapsed after BoNT-A injection. Therefore, repeated injections provided a longer therapeutic duration.

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Conflicts of interest

Dr. Yuan-Hong Jiang and Hann-Chorng Kuo, the editorial board member at *Tzu Chi Medical Journal*, had no role in the peer review process of or decision to publish this article. The other author declared no conflicts of interest in writing this paper.

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