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CLINICAL OPINION

Trigone as a diagnostic and therapeutic target for bladder-centric interstitial cystitis/bladder pain syndrome

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Abstract
The pathophysiology of interstitial cystitis/bladder pain syndrome (IC/BPS) may be bladder-centric, with afferent nerve hyperexcitability and/or due to neural central sensitization. In bladder-centric disease, the trigone's unmyelinated nociceptive C-fibers are thought to be upregulated, suggesting this as a potential target for diagnostic modalities and for treatment with local anesthetics and chemodenervation. We propose that the transvaginal trigone treatment (T3) route of administration of such treatments should be considered in women with IC/BPS, as this approach is easier and less invasive than cystoscopy. For T3, or other bladder-centric treatments to be successful, patient selection should attempt to exclude patients with predominantly neural central sensitization.

Keywords Female · Interstitial cystitis · Urinary bladder · Afferent pathways · Type A botulinum toxins · Local anesthetics

Categorizing IC/BPS patients by pathophysiology

Interstitial cystitis/bladder pain syndrome (IC/BPS) is a debilitating chronic pain condition that affects 3.3 to 7.9 million women in the USA [1]. Like most chronic pain syndromes, it lacks a single finite remedy, leading to frustration for patients and physicians alike, and off-label, inadequately tested therapies. Development of effective treatments has been hampered by limited understanding of the pathophysiology and poor classification of patients, the latter resulting in suboptimal clinical trial design and failure of regulatory approval of new treatments. The two FDA-approved treatments: intravesical dimethyl sulfoxide (DMSO, Rimso-50®) and oral pentosan polysulfate sodium (Elmiron®) are old, having been approved in 1978 and 1996 respectively, and are less commonly used today because of poor long-term efficacy, significant side effects, and challenges of drug delivery.

Because clinicians treating IC/BPS appreciate the potential for both local and central components of the disease, they often resort to multimodal therapy, combining bladder-centric treatments with anxiolytics, antidepressants, and systemic analgesics [2]. This creates a regulatory minefield when designing studies for market authorization. Consequently, recent monotherapy clinical trials aimed at treating bladder pathology in IC/BPS have failed to lead to drug approval because they have not attempted to define a subset of bladder-centric patients. We argue that development of novel bladder-centric therapies for IC/BPS requires appropriate patient selection, specifically identifying a group with predominantly bladder-centric disease. How might we make this diagnosis in our patient population?

Once there has been significant central nervous system dysregulation resulting in sensitization and exaggerated pain perception in response to external stimuli [3], bladder-centric treatment has a lower chance of success. Although this might be an oversimplification, we suggest that bladder-centric disease should respond to pharmacological treatments targeting the trigone and central neural sensitization should be treated with psychotherapy and adjuvant pharmacotherapy. This again stresses the importance of patient selection for any given treatment approach in the context of clinical trials needed for regulatory approval.

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Neurophysiology

The bladder dome and trigone have different innervation and this regional distribution lends itself to anatomically targeted therapy. Basic science research shows that the trigone and bladder base are populated by small unmyelinated afferent nociceptive C-fibers that are upregulated in IC/BPS [4]. These C-fibers are probably responsible for the transduction of pain and urgency, but appear to have no role in normal bladder function. Teleologically, it could be argued that they exist to respond to noxious stimuli such as infection by encouraging the host to have urinary frequency and hence aid the expulsion of the infective organism. The rest of the bladder is populated with A-delta (afferent) and parasympathetic (efferent) nerves that allow recognition of the sensation of bladder fullness and detrusor contraction respectively [5]. Therapeutic interventions should ideally treat just the pathophysiology while preserving normal physiology. Selective targeting of the upregulated C-fibers in the trigone and not the other neural supply of the bladder, might have utility for diagnostic and therapeutic purposes.

Possible diagnostic tools

Bimanual pelvic examination in women

Patients with IC/BPS are very sensitive to genital manipulation; therefore, pelvic examination should be done slowly, and preferably while diverting the patient's attention away from the examination by discussing areas of interest to the patient and asking her to answer open-ended questions that require thoughtful responses. While the patient is so distracted, the examiner can gently palpate the introitus, levator ani muscles, and the anterior vaginal wall under the urethra and trigone. If maximum tenderness is elicited by urethral and bladder palpation and on abdominal palpation of the bladder, the patient is likely to have bladder-centric disease. Unfortunately, such subjective evaluation is easily prone to error.

Anesthetic bladder capacity

A preliminary report showed that patients with bladder-centric disease are thought to have lower anesthetic bladder capacity (<400 ml) during hydrodistension [6]. In this retrospective review of 110 IC/BPS patients who underwent hydrodistension, it was noted that bladder capacity showed significant inverse correlation with the Interstitial Cystitis Symptom and Problem Index and the Pelvic Pain and Urgency/Frequency Patient Symptom Scale. Women with higher bladder capacity were significantly more likely to report depression and irritable bowel syndrome. Clearly, these data need to be corroborated by prospective studies, but the conclusions are logical and cogent.

Neurometry

Neurometry measures the current perception threshold (CPT) of different nerve fiber types. Nerves of different diameters respond to different frequencies of stimulation and the threshold of response by the patients' perception of sensation, which reflects sensitivity, is thought to be a measure of fiber density. Therefore, this technique could be a useful diagnostic tool and could also serve as a biomarker to investigate selective neuromodulation techniques. C-fibers (small unmyelinated nerves) can be stimulated with lower frequencies, whereas A-delta fibers (larger myelinated nerves) require higher frequency stimulation [7]. Consequently, this technique could be used to identify those patients with up-regulated C-fibers in the trigone, implying bladder-centric disease. Commercially available catheter-mounted electrodes can be inserted via the urethra into the bladder and the location of the tip (electrode) confirmed by ultrasound. In this way, CPT recordings can be made from the trigone or the dome of the bladder [8]. Unfortunately, many IC/BPS patients will find this technique too uncomfortable, thus limiting its widespread use.

Lidocaine

Intravesical lidocaine instillation is successful in relieving acute episodes of IC/BPS, but therapeutic utility is challenged owing to a short duration of action, necessitating frequent repeat instillations [9]. Given the poor penetration of lidocaine through the urothelium, an injection into the trigone would be an option, but doing so via a cystoscopy is excessively invasive as a diagnostic test. However, the trigone could be injected less invasively via the anterior vaginal wall (see below). This lidocaine challenge test could be used diagnostically to identify IC/BPS patients with bladder-centric disease, although they may also have central sensitization.

Small fiber polyneuropathy

Small fiber polyneuropathy (SFPN) is associated with fibromyalgia, which is also associated with IC/BPS. A pilot study of 11 women with IC/BPS underwent distal leg skin biopsies and immunostaining to identify those with SFPN. Four patients were considered to have bladder-centric disease as they had anesthetic bladder capacity of <400 ml during hydrodistension [6]. Bladder-centric patients had significantly less SFPN than the other IC/BPS patients, suggesting that this technique could serve as a biomarker for diagnosing patients with central sensitization if the data are confirmed by larger studies [10].

Bladder-centric index

Although the above discussion has identified several ways of identifying bladder-centric disease, it is not clear which diagnostic tools would offer the greatest discrimination. It is also possible that each individual diagnostic test may have suboptimal utility, but, taken together, these tests as a group may offer a more accurate diagnosis. To achieve this, a large prospective study of patients with IC/BPS needs to be performed where all these criteria are examined, with an intent to construct a bladder-centric IC/BPS index that weights each component optimally. Although laborious and expensive, such an exercise would be well worth it if it allowed prognostication and hence effective personalized medical care of these patients.

The optimal route of administration of "local" treatments

Introduction

Given the predominance of upregulated nociceptive C-fibers located in the trigone in functional disorders of the bladder such as OAB, neurogenic bladder, and IC/BPS [3, 5], it makes sense to select the trigone for such local treatment. However, in their approval of botulinum toxin A (BTA) for treatment of OAB, the FDA approved the technique that involves 20 intra-detrusor injections into the posterior-lateral aspects of the bladder, sparing the trigone. Although effective, this treatment leads to the side effects of impaired voiding manifesting as retention of urine, increased urinary tract infection (UTI), and dysuria rates, thus limiting its use to women who are willing to self-catheterize. Similar to published clinical trials [11–14], for many patients with IC/BPS, office cystoscopy is not tolerable and necessitates general anesthesia in the operating room (OR) in order to allow adequate bladder distension and needle penetration of the urothelium. Utilization of BTA in IC/BPS is limited, as for many of these patients, the side effects are unacceptable.

Trigone-sparing injections

The original trigone-sparing technique was proposed because of concerns that injecting BTA near the ureteric orifices would result in reflux. However, several investigators have refuted this [15]. In fact, some have suggested including the trigone results in improved efficacy [11].

We suggest that the therapeutic effect of intra-detrusor BTA in IC/BPS is due to diffusion from the posterior-lateral sites of injection back to the trigone. It is known that BTA spreads from the site of injection and a significant proportion of it can be seen with magnetic resonance imaging to be outside of the bladder wall owing to extensive diffusion [16]. We postulate that the optimal site of BTA injection is the trigone in IC/BPS.

Trigone-only injection

Researchers from Taiwan have reported data on cystoscopically injecting BTA in patients with refractory OAB, comparing trigone only with trigone-sparing approaches. They found that the efficacy was similar, but the side effect profile was improved in the trigone-only group; in particular, they had no cases of urinary retention [17]. This technique has also been shown to be efficacious in IC/BPS patients but with a superior safety profile. In a retrospective analysis, we compared a single trigone-only injection with a standard FDA-approved technique of 20 trigone-sparing injections using 100 units of BTA in refractory OAB. The durability, as determined by the inter-injection interval, was similar in the two groups. However, the trigone-only procedure was quicker and resulted in lower postvoid residual (PVR) and rates of urine retention requiring catheterization. There were no cases of ureteric reflux. Several uncontrolled studies have documented the efficacy of cystoscopic BTA injections in the treatment of IC/BPS and several randomized controlled trials (RCT) have demonstrated the same [12–14]. However, none compared the trigone-only against the trigone-sparing effects of BTA.

There has only been one report of a placebo-controlled RCT of trigone-only treatment in IC/BPS [11]. In this RCT of 21 women, at 12 weeks, pain reduction with BTA was −3.8 [± 2.5] versus −1.6 [± 2.1] for controls; thus, significantly better ($p < 0.05$). Further, 60% of BTA subjects had a 50% or greater reduction in pain on the visual analog scale versus 22% for placebo. The authors also found significant improvements in the O'Leary-Sant questionnaire, quality of life, and treatment benefit scale scores with BTA. There was no urinary retention and the small number of patients with UTI all had normal PVRs, suggesting that cystoscopy itself was the cause of the UTI rather than impaired detrusor contractility due to BTA treatment.

In conclusion, there is mounting evidence that BTA injections are effective in IC/BPS and that trigone-only injections are also effective, but they may have a more benign side effect profile.

The transvaginal approach to the trigone

Trigonal treatment with BTA is effective, but accessing the bladder via the cystoscope is cumbersome and in IC/BPS patients such manipulation would necessitate treatment in the OR. Anatomically, the anterior vaginal wall is adherent to the overlying trigone and is ~4 cm proximal to the introitus and therefore easily accessible via the vagina [18]. The entire area of the trigone is only ~3 cm^2 [18]; thus, a single injection through the anterior vaginal wall should suffice for treatment of the entire trigone (Fig. 1). The vesico-vaginal wall thickness at the trigone (VVWTT) is 10 ± 2 mm based on our analysis of published

ultrasound measurements [19, 20]. Therefore, the needle needs only to penetrate to about 5 mm and the volume of injection can be significantly reduced given that the volume of tissue to be injected is only approximately 3 cm^3.

We have demonstrated the feasibility of this transvaginal trigone treatment (T3) technique in female cadavers [21] using laparoscopy and ultrasound (Fig. 2). In women with OAB we have performed 10 injections in the office without anesthesia via visual landmarks, confirmed by ultrasound guidance. The visual appearance of the vaginal rugae on the anterior vaginal wall are used to define the position of the overlying bladder neck and so injections placed 1.5 cm proximal from the bladder neck result in BTA being injected into the middle of the trigone. Post-injection, to confirm accurate placement, vaginal ultrasound was used to measure VVWTT, which increased from a mean of 6.4 ± 1.0 mm before injection, to 9.6 ± 1.5 mm post-injection, with the increase ranging from 2.1 to 5.8 mm, indicative of correct BTA placement in all cases. The procedure was very well tolerated without local anesthetic, with a mean procedure pain score of 2.4 ± 1.6 (numerical rating scale, range 0 to 10). Improvement in the treatment benefit scale was noted in 80% at 6 weeks and 71% at 12 weeks, which is slightly better than that reported in the BTA phase III OAB trials, indicative of comparable efficacy. No patient-reported adverse effects were directly attributed to the transvaginal route and no women experienced retention of urine.

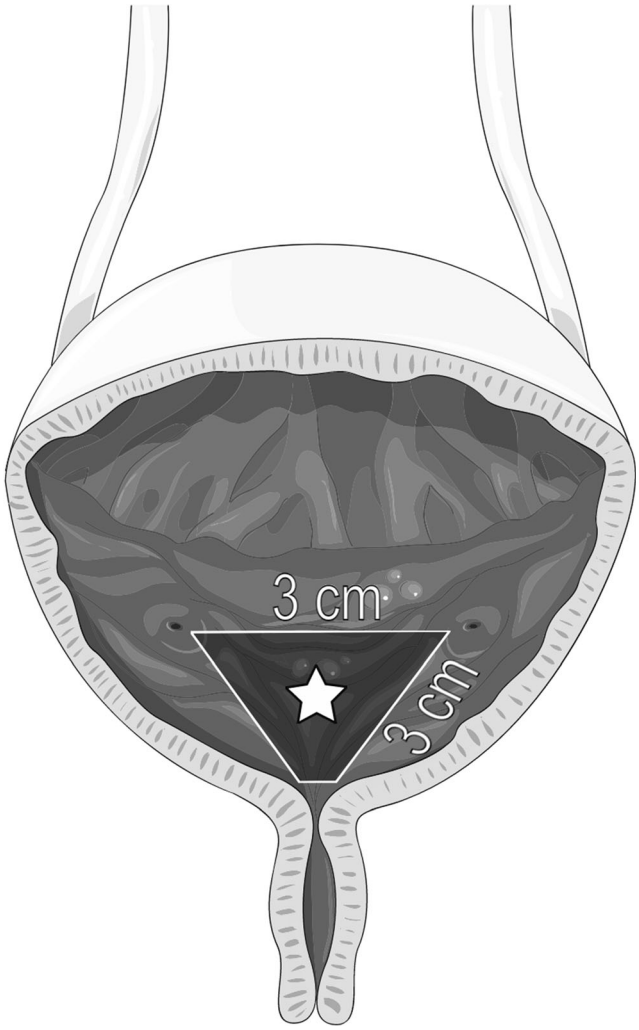

Fig. 1 Dimensions of the trigone in female cadavers. *Star* indicates the site of transvaginal trigone treatment with botulinum toxin A injection. Image created from Servier Medical Art by Servier, which is made available under the terms of the Creative Commons Attribution 3.0 France license

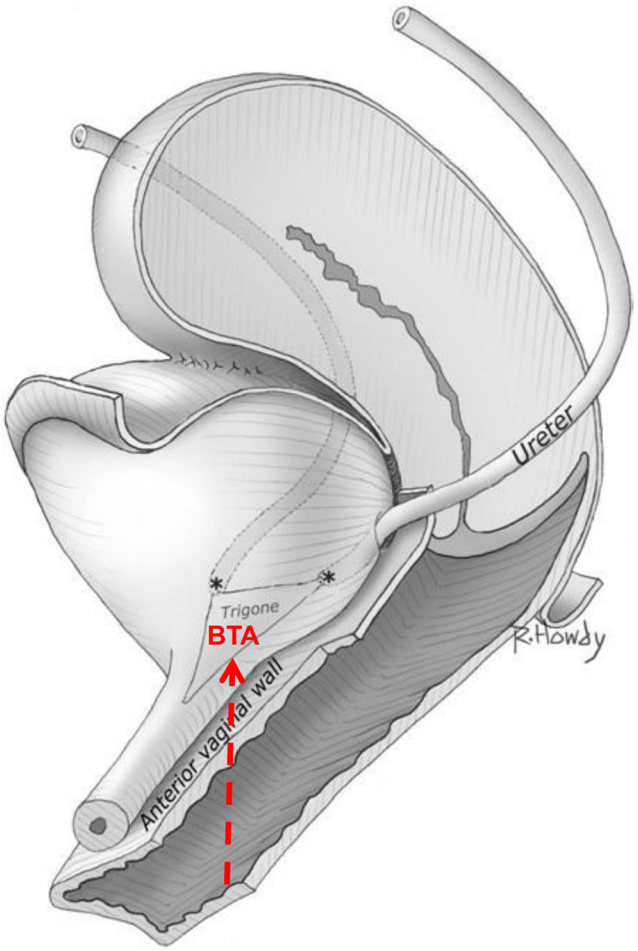

Fig. 2 Anatomy of the trigone and trajectory of needle insertion (*arrow*) to deliver botulinum toxin A (BTA) via the transvaginal trigone treatment approach. Image adapted from Rahn et al. [18], with permission (RightsLink license number 5025500203603)

The utility of transvaginal trigone treatment

Office diagnosis

The T3 approach is simple and non-invasive and is an ideal technique for a local anesthetic diagnostic test. In IC/BPS patients, if a lidocaine injection transiently eliminated symptoms it would imply that local BTA was likely to succeed as

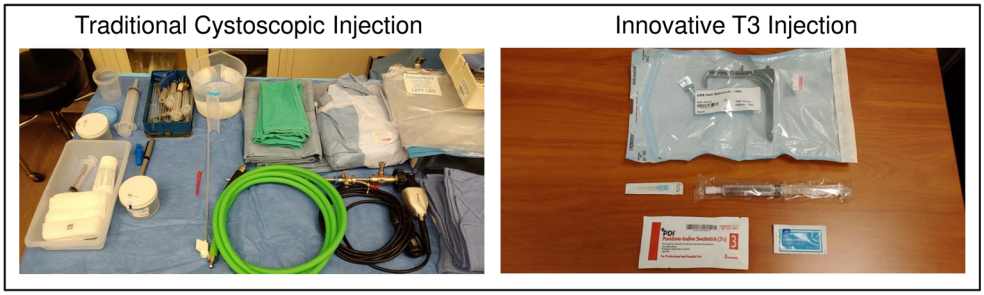

Fig. 3 Comparison of equipment required for traditional cystoscopic botulinum toxin A (BTA) injection in the operating room under general anesthesia, versus the innovative transvaginal trigone treatment (T3) route of BTA delivery, for women with interstitial cystitis/bladder pain syndrome

long-term therapy. In fact, this concept was proposed by work from McGuire's group [22] who showed that this was a prognostic indicator for success with the modified Ingelman-Sundberg bladder denervation procedure. There have been unpublished anecdotal reports of T3 lidocaine injection use following hydrodistension to reduce postoperative pain (Dr. Robert Evans and Dr. Amy Dobberfuhl, personal communication).

Lidocaine and BTA injection for acute and chronic treatment of IC/BPS

Simple patient-acceptable office treatment for IC/BPS could be T3 injection of lidocaine and bupivacaine as an immediate treatment for flares and could confer relief in a matter of minutes that lasts for several hours. Given the anti-inflammatory effects of these local anesthetics, this treatment might interfere with neuroinflammation during an IC/BPS flare and hence reduce its duration. This could necessitate just one or two T3 injections per flare. Obviously, this hypothesis requires testing in the clinic. Phenazopyridine and intravesical instillations are not ideal options for immediate long-lasting pain relief in a woman with IC/BPS experiencing a flare. Given the severity of the pain, opiates are often prescribed, but as systemic treatment they incapacitate the individual and increase the risk of addiction.

Although effective in the long term, intradetrusor BTA injections are too painful in many IC/BPS patients to be performed in the office via cystoscopy. This opinion is supported by our survey of the literature that revealed the majority of BTA treatments for IC/BPS are performed in the OR with anesthesia [11–14]. This is primarily due to cystoscopic manipulation. Obviously, one T3 injection compared with 20 cystoscopic injections into the posterior-lateral detrusor is intuitively likely to be more comfortable. If feasible, this would significantly increase utilization, be less expensive, and much more tolerable. This hypothesis needs testing. In terms of cost reduction, the greater equipment requirements for administration of BTA in the OR under anesthesia versus the T3 approach are shown (Fig. 3). The cystoscopic BTA procedure is technically demanding and equates to 24 to 37 min of physician reimbursement billing time for cystoscopy alone [23], not accounting for BTA-specific equipment setup, intravesical instillation of lidocaine, procedure clean-up, and the costs associated with general anesthesia. Moreover, from the woman's perspective, the more formal procedure is often frightening, which also contributes to underutilization. Even in non-IC/BPS patients, cystoscopy can be very uncomfortable, as 15% of patients develop urethrorrhagia and dysuria following cystoscopy [24]. In contrast, a single T3 injection would not be so uncomfortable nor would it predispose to UTI.

BTA injection for OAB

The arguments above are equally applicable to OAB. Despite the obvious clinical efficacy of BTA in OAB, 26.5% of women fail to seek additional treatment beyond their first injection, possibly as a result of the consequences of the cystoscopic route of delivery, namely increased risk of UTI, and urinary retention [25]. We have anecdotal experience that shows that transvaginal injection of local anesthetics in awake IC/BPS patients is feasible. Our pilot experience in OAB patients suggests that delivering BTA via the T3 approach may obviate the need for general anesthesia, use of the OR and pre-treatment with lidocaine. Further, the T3 approach would require just a single injection rather than the standard 20 injections and could be administered by a single operator without staff to assist. Clearly, properly conducted clinical trials are required to substantiate these hypotheses.

Conclusions

The pathophysiology of IC/BPS can be regarded as bladder-centric and/or neural central sensitization. It is critical to determine the contribution of each to allow for appropriate patient selection for successful outcomes in clinical trials and practice. There are several strategies that can be employed to aid patient selection, but most clinical trials to date have not made a thorough attempt, which might explain why so many have failed and why no new therapies have been approved by the FDA since 1996. Experimental verification of these strategies is needed to determine if a single approach will work or

if an index constructed out of the different modalities is needed to accurately define a population of patients with bladder-centric disease.

The trigone appears to be the site of upregulated nociceptive C-fiber afferents, suggesting it to be the target of bladder-centric treatments. In women, this is more easily accessed via the vaginal route (T3) rather than through the cystoscope. This simple technique could be used for diagnostic purposes, but also for treatment of acute flares or more long-term treatment of IC/BPS using BTA.

These suggestions and conclusions are the authors' opinion, but our goal of publishing these ideas is to stimulate debate and engage researchers to examine these proposed hypotheses critically and experimentally in the hope of improving treatments and the lives of patients with IC/BPS.

Abbreviations BTA, Botulinum toxin A; CPT, Current perception threshold; IC/BPS, Interstitial cystitis/bladder pain syndrome; OAB, Overactive bladder; OR, Operating room; PVR, Postvoid residual; RCT, Randomized controlled trial; SFPN, Small fiber polyneuropathy; T3, Transvaginal trigone treatment; UTI, Urinary tract infection; VVWTT, Vesico-vaginal wall thickness at the trigone

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Declarations

Conflicts of interest A. Dobberfuhl is an investigator for the SUFU Foundation seed grant entitled "Feasibility and efficacy of transvaginal onabotulinumtoxinA chemodenervation of the trigone for the third line treatment of refractory overactive bladder." S. van Uem declares no conflicts of interest in relation to the content of the manuscript. E. Versi is the inventor of patent USPTO #8,029,496 entitled "Method and device for delivering drug to the trigone of the bladder" and consultant for Hologic Inc.

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