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Review Article

Botulinum Toxin A in the Treatment of Interstitial Cystitis/Bladder Pain Syndrome: A Short Review

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Abstract

Interstitial Cystitis/Bladder Pain Syndrome (IC/BPS) is a chronic and debilitating condition that negatively impacts quality of life. Several causes have been postulated in the pathogenesis of this condition; however, the aetiology remains unknown. IC/BPS may go undiagnosed for many years because the condition often co-exists with other chronic pain syndromes. Furthermore, the symptoms of IC/BPS vary considerably across patients, therefore no one treatment has shown to be consistently effective in providing relief. Thus, the goal of management of IC/BPS remains to provide relief of symptoms in order to improve a patient's quality of life. Intravesical Botulinum toxin A (BoNT-A) is emerging as a potential new pharmacologic treatment for IC/BPS refractory to conventional treatment modalities. However, there is vey few data supporting the efficacy of this treatment. The aim of our short review is to assess the efficacy of intravesical BoNT-A in IC/BPS.

ABBREVIATIONS

IC/BPS: Interstitial Cystitis/Bladder Pain Syndrome; BoNT-A: Botulinum Toxin A

INTRODUCTION

Interstitial Cystitis/Bladder Pain syndrome (IC/BPS) is a clinical diagnosis primarily based on the symptoms of urinary urgency, frequency, nocturia and pain in the bladder or pelvis related to bladder filling [1,2]. This occurs in the absence of proven urinary tract infection or other obvious pathology. This condition is chronic and can be severely debilitating and has a negative impact on the quality of life of patients [3,4]. Although several causes have been postulated in the pathogenesis of IC/BPS, including infection, autoimmune reaction, neurogenic inflammation, urothelial dysfunction and inherited susceptibility, the actual aetiology remains unknown [5]. The prevalence of IC/BPS often tends to be underestimated [6]. IC/BPS occurs five times more commonly in women than men [7]. A comprehensive epidemiology study concluded that between 2.7 and 6.5 percent of United States women have symptoms consistent with IC/BPS [7].

Due to a lack of understanding of the aetiology of IC/BPS and the variability of symptoms among patients, no one treatment has shown to be consistently effective in providing relief. This was illustrated by the Interstitial Cystitis Data Base study, in which women underwent different types of therapy over several years of follow-up, no single therapy was found to be successful in most patients [8]. Consequently management is often directed at pain relief and improving quality of life. Intravesical Botulinum toxin A (BoNT-A) is emerging as a potential new pharmacologic treatment for patients with IC/BPS refractory to conventional treatment modalities. Our aim in this review is to assess the efficacy of intravesical BoNT-A in IC/BPS.

Diagnostic approach of IC/BPS and clinical features

The goal of diagnostic evaluation for IC/BPS is to identify characteristic features and exclude other conditions. The evaluation includes a careful history to elicit the symptoms and associated conditions, physical examination and urine analysis to exclude infection and haematuria. Baseline voiding symptoms and pain levels should be obtained using validated symptom scales such as the IC Symptom and Problem Index and Genitourinary Pain Index to assess symptom severity and measure subsequent treatment [9,10]. Cystoscopy and/or urodynamics are not required to make a diagnosis of IC/BPS. They are typically considered when there is clinical uncertainty about the diagnosis. Cystoscopy can be used to identify conditions such as bladder cancer and foreign bodies, additionally Hunner's ulcer which is a typical cystoscopic finding in 10-15% of patients with IC/BPS may be demonstrated [11]. Urodynamics may be indicated if there is suspicion of bladder outlet obstruction or neurogenic

dysfunction. These tests are not necessary in uncomplicated presentations. It is also important to note that IC/BPS does not have any characteristic findings on medical imaging.

IC/BPS may go undiagnosed for many years, especially in mild or moderate disease. This is because the condition often co-exists with other chronic pain syndromes including fibromyalgia, irritable bowel syndrome and vulvodynia. Additionally, symptoms can overlap with other gynaecological conditions including dysmenorrhoea and endometriosis and urologic conditions like bladder and urethral cancer. As a result this often makes the diagnosis of IC/BPC difficult [2,12].

The symptoms that tend to differentiate IC/BPS from other conditions are pelvic pain usually described as suprapubic or urethral and the most consistent feature being an increase in discomfort with bladder filling and a relief with voiding [13,14]. Urinary incontinence is not a typical feature of IC/BPS [11]. Regarding the onset of symptoms, patients often describe symptoms to be of gradual onset associated with worsening discomfort, urgency, frequency and nocturia over a period of months.

Mechanism of effect of BoNT-A therapy

BoNT-A is a potent neurotoxin derived from the anaerobic bacterium *Clostridum botulinum*. The mechanism of action of BoNT-A is likely due to its ability to modulate sensory neurotransmission and reduce neurogenic inflammation. This is done by impairing the release of neuropeptides such as such as substance P, calcitonin gene related peptide and glutamate, which are all involved in pain transmission from either dorsal root ganglion neurons, sensory afferents nerves and/or urothelial cells [15,16]. Hence by decreasing noxious input BoNT-A assists in providing analgesic effects, thus improving voiding frequency and nocturia [17,18].

One of the major advantages of intravesical BoNT is that it establishes high concentrations with few systemic side effects [19]. However, a potential disadvantage of BoNT-A administration is that the post void residual may increase and that there is a significant risk of urinary retention [18,19]. This may be especially devastating to a patient with painful bladder. Thus a patient who is considering having intravesical BoNT should be informed for the possibility of urinary retention and must also be willing and able to perform intermittent self catheterisation.

Efficacy of BoNT-A

There is few data regarding the efficacy and safety of BoNT treatment for IC/BPS. The best available data are from a small randomised controlled trial conducted by Kuo and colleagues 2009 [20]. In this study 67 patients were randomised to suburothelial injection of BoNT-A (100 U or 200 U) group combined with hydrodistension or to hydrodistension alone. The BoNT-A groups had a significantly higher proportion of patients with moderate or marked improvements in symptoms at six months (71 versus 48 percent). This difference was maintained at 12 and 24 months follow up (55 versus 26 percent) and (30 versus 17 percent) respectively. The appropriate dose of BoNT-A, however, was not determined. Several patients in the 200 units group had adverse reactions including acute or chronic urinary retention or severe dysuria. For this reason the dose was then decreased to 100 units. With 100 units the number of adverse events reduced but still occurred more frequent with hydrodistension alone.

Another study by Kuo 2013 examined the efficacy and safety of repeated intravesical BoNT-A. In this study thirty-one patients had a combination of 100 U of intravesical BoNT-A injection with cystoscopic hydrodistention under general anaesthesia. Four sessions of BoNT-A intravesical injections were shown to be safe and effective. Long term pain relief was recorded in 61% of the patients with IC/BPS who were refractory to conventional treatment. However, patients with Hunlner's ulcer were poor candidates for this combined treatment [21]. Similarly, this finding was also concluded in a recent study conducted among 81 patients [22]. The study demonstrated significantly better success rates in patients who received 3 or 4 repeated injections of 100 U intravesical BoNT-A, compared to those who received a single injection. Furthermore, there was no significant difference ($p=0.235$) in occurrence of adverse events such as urinary tract infection, acute urinary retention and dysuria after repeated BoNT-A injections.

According to a study conducted by Pinto and colleagues 2010, the incidence of voiding dysfunction may be reduced by restraining BoNT-A to the trigone rather than injecting the whole bladder [16]. This is because as a fixed part of the bladder, predominantly innervated by sympathetic nerves the trigone does not contract during voiding [23]. Furthermore, by using only 100 units of BoNT-A the potential risk of complications can be further reduced. In this study and no cases of voiding dysfunction were reported. It is evident that further study is required on a larger cohort of patients in order to determine the optimal dose of BoNT-A and ideal location(s) for application so that patients experience optimal symptomatic relief and without significant complications.

Observational studies suggest that BoNT-A is associated with an improvement in symptoms in a subset of patients with IC/BPS. These symptoms gradually return to base line over six to nine months therefore repeated doses are often needed to maintain effective control of bladder pain and urgency [23-28]. However, if BoNT-A is used in conjunction with other modalities such as hydrodistension, as demonstrated in studies conducted by Kuo and colleagues and Chung and colleagues 2012, rather than BoNT-A alone, patients may experience longer symptomatic relief. The characteristic findings of all the studies are summarised (Table 1).

CONCLUSION

In conclusion IC/BPS is a chronic condition that often exists with other pain syndromes. It also negatively impacts on the quality of life of patients. Its aetiology remains unknown and no one treatment has been shown to be consistently effective in providing relief. BoNT-A appears to provide effective, short term relief for a subset of patients. The beneficial effects, however, progressively decrease within a few months after treatment. Thus repeat injections of the neurotoxin are required. Further

Table 1: Characteristics of the included studies.

Primary author, publication date	Participants	Methods and duration of follow up	Regimen	Outcome measures	Effectiveness	Complications reported
Kuo HC 2005	10 patients (8 women and 2 men) with chronic IC/ BPS diagnosed based on characteristic symptoms and cystoscopy findings	Prospective study with 3 month follow up	BoNT-A dose: 100-200 U Injection site: 5 patients had 100 U suburothelially into 20 sites on posterolateral bladder walls; 5 patients had additional 100 U injected into 5 sites of the trigone Cystoscope: rigid Anaesthesia: general anaesthesia (GA)	3-day voiding dairy, 5-point scoring system for pain, urodynamics at baseline and 3 months post treatment	At 1 month: 2 reported improvement in bladder pain and urinary frequency At 3 months: Statistically significant improvement in cystometric bladder capacity (p=0.05), urinary frequency (0.025)and pain score (p=0.003) Trigomal injection had no effect on symptom or urodynamic improvement	100% experienced dysuria, frequency, urgency exacerbation in first 3 days after treatment Mild difficulty with urination in first month reported in 70% of patients and 4 had post void residual (PVR)>100ml
Giannantoni A 2008	17 patients (12 women and 3 men) with IC/ BPS diagnosed based on linical symptoms and sterile urine	Prospective non-randomised study with 1 year follow up	BoNT-A dose: 200 U Injection site: submucosally in bladder lateral walls and trigone Cystoscope: rigid Anaesthesia: GA	Voiding chart, visual analogue scale (VAS), for pain and urodynamics pre and post-op (1, 3, 5 and 12 months)	At 1 and 3 months: 13 patients (86.6%) reported subjective improvement. At 3 months: VAS, daytime and night time urinary frequency significantly decreased (p<0.05, <0.01 and <0.05 respectively) At 5 months: Bladder pain recurred in 73.3% of patients and beneficial effects persisted in 26.6% of patients At 12 months pain recurred in all patients	Dysuria: 60% at 1 month, 27% at 3 months and 13% at 5 months Clean intermittent self-catheterisation (CISC): 20% at 24 hours, 13% at 3 months 1 patient at 5 months
Kuo HC 2009	70 patients 67 patients analysed (56 women and 11 men) BoNT-A group: 44 (15 patients 200 U; 29 patients 100 U) Control group (HD): 23 Dropouts 3 All patients had been treated with conservative treatment for greater than 6 months without response	Randomised controlled trial to compare effectivenss of BoNT-A injections followed by hydrodistension (HD) with HD alone BoNT-A group: 200 or 100 U of BoNT-A followed by cystoscopic HD 2 weeks later Control group received identical HD without BoNT-A 60% of the patients in 200 U BoNT-A group developed complications, thus the study protocol was changed at 1 year and 40% patients were reassigned to 100 U BoNT-A group	Treatment group: BoNT-A dose: 100 U or 200 U Injection site: suburothelially at 40 sites in posterolateral bladder walls. 5 and 2.5 U in 0.5ml per site in 200 and 100 U BoNT-A respectively Cystoscope: rigid Anaesthesia: GA	3-day voiding diary, O'Leary-Sant score (OSS), functional bladder capacity (FBC), VAS for pain, global response assessment (GRA) and urodynamic studies at baseline and 3 months post HD Primary end point was assessment at 3 months after HD and follow up at 3 month intervals until recurrence of symptoms Patients with moderate to marked improvement on a 7 point GRA were considered to have a successful outcome	GRA improvement at 3 months: BoNT-A 200 U group 80% of patients BoNT-A 100 U group 72% of patients HD group 48% of patients At 3 months: OSS scores decreased significantly in all three groups VAS reduction, significant increases in FBC and cystometric bladder capacity significant only in BoNT-A groups Beneficial effect persisted in 71% of patients at 6 months. Successful result at 12 and 24 months was reported in 55% and 30% of BoNT-A group, respectively compared with only 26% and 17% in control group (p=0.002) 9 of 15 patients in BoNT-A 200 U group developed complications, thus the study protocol was changed at 1 year and 6 patients were reassigned to BoNT-A 100 U group	BoNT-A 200 U group vs BoNT-A 100 U group UTI: 20% vs 0% Haematuria: 13% vs 0% Dysuria: 47% vs 10% 1 in HD group Large PVR: 33% vs 7% Acute urinary retention: 13% vs 3%

Rui A. Pinto 2010	26 females	Single centre prospective study with 10 patients followed for 6 months and 16 patients followed for 2 years	BoNT-A dose: 100 U Injection site: trigone only, 10 injections each containing 10 U in 10ml normal saline Anaesthesia: GA	O'Leary-Sant score (OSS), voiding chart, quality of life (QOL) from IPSS, urodynamic testing at 1 and 3 months and every 3 months thereafter, urine nerve growth factor (NGF) and brain derived neurotrophic factor (BDNF)	At 1 and 3 months: Pain , daytime and night-time voiding frequency, OSS, QOL improved significantly ($p<0.05$) Bladder volume to first pain and maximal cystometric capacity more than doubled Significant reduction in NGF and BDNF was observed at 1 month ($p<0.05$) Treatment remained effective in >50% of patients for 9 months	No cases of voiding dysfunction and infection
Chung SD 2012	67 patients (60 women and 7 men) with IC/BPS who had failed conventional treatment for at least one year Diagnosis based on characteristic symptoms and cystoscopic findings	Prospective non-randomised study with follow up every 3 months for 6 months	BoNT-A dose: 100 U followed by cystoscopic hydrodistension Injection site: each vial diluted in 20 ml normal saline; 40 suburothelial injections made Cystoscope: rigid Anaesthesia: GA	3 day voiding diary, O'Leary-Sant Cystitis Problem Index (ICPI), interstitial cystitis symptom index (ICSI), VAS pain score, urodynamic study	3 and 6 month follow up: Bladder pain, ICPI, ICPI, functional bladder capacity improved significantly from base line at 3 and 6 month follow up ($p=0.000$) Post void residual also improved significantly from baseline ($p=0.002$)	Dysuria 36% of patients Urinary tract infection 6% of patients No patients needed clean intermittent self-catheterisation No episode of acute urinary retention
Kuo HC 2013	81 patients with IC/BPS who failed conventional treatments, diagnosis was established on characteristic symptoms and cystoscopic findings	Prospective interventional study, follow up every 6 months	BoNT-A dose: 100 U every 6 months for up to 4 times or until patients' symptoms improved significantly Among 81 patients: 20 received single injection, 19 received 2 injections, 12 received 3 injections and 30 received 4 injections Injection site: Each vial of BoNT-A was diluted with 20 ml normal saline and 40 suburothelial injection made Cystoscope: rigid Anathesia GA	ICSI, ICPI, VAS for pain, voiding diary, urodynamic study, global response assessment	Significantly better success rates were noted in patients who received 4 repeated injections ($p=0.0242$) and 3 injections ($p=0.05$) compared with those who received a single injection No significant differences of long-term success rates among patients who received 2, 3 and 4 injections ($p>0.05$)	Dysuria: 30% of patients had dysuria after each BoNT-A One episode of aute urinary retention and clean intermittent self-catherisation Urinary tract infection: developed in 4.9 to 19% of patients after each BoNT-A treatment Occurrence of adverse events did not increase with increasing number of BoNT-A injection ($p=0.235$)

Manning J 2014	54 women with IC/BPS who had failed two or more recognised treatments 1 withdrawn pre randomisation due to bladder cancer AboBTXA group + HD group: 26 Saline + HD group: 27	Randomised double blinded study, patients were followed up for at least 2 years for some patients (at 1 week, 6 weeks and then 3 monthly) Abobotulinumtoxin (AboBTXA) group: 500 U of AboBTXA (equivalent to approximately 2 to 2.5 ampoules of Botox 100 U) with HD Control group: 30 ml of normal saline into bladder and HD Patients and doctors were blinded to initial treatment. Patients with no improvement after initial treatment had access to AboBTXA at a minimum of 3 months, but remained blinded to original treatment	AboBTXA dose: 500 U (equivalent to 2 to 2.5 ampoules of Botox 100 U) Injection site: 30 sites paring the trigome and ureters Anaesthesia: GA	OSS (consists of ICPI, ICSI), bladder diary (assessing fre)quency, nocturia and voiding difficulty, urodynamic study	3 month follow up (AboBTXA+HD vs saline+HD) AboBTXA showed a significantly greater improvement in ISPI at 3 months (p=0.04) than control group No improvement in the total OSS scores for both groups at 3 months 78% of the control group requested AboBTXA at 3 months, compared with 62% of initial AboBTXA patients (this is not a significant difference p=0.16) Data regarding further follow up not provided	Urinary tract infection: 27% of AboBXTA group vs 19% of control group (despite baseline negative urine culture and preioperative antibiotics)

Abbreviations: PVR: Post Void Residual; VAS: Visual Analogue Scale; OSS: O'Leary-Sant Score; FBC: Functional Bladder Capacity; HD: Hydro Distension; QOL: Quality of Life; NGF: Nerve Growth Factor; BDNF: Brain Derived Neurotrophic Factor; ICPI: O'Leary Cystitis Problem Index; ICSI: O'Leary Cystitis Symptom Index

studies are warranted in order to determine the ideal dose of BoNT-A and location to apply at so patients receive maximal symptomatic relief without significant complications.

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