Int Urogynecol J (2010) 21:1285–1300
DOI 10.1007/s00192-010-1162-9

REVIEW

Intravesical botulinum toxin A injections in the treatment of painful bladder syndrome/interstitial cystitis: a systematic review

Sahithi Tirumuru · Deyaa Al-Kurdi · Pallavi Latthe

Received: 31 January 2010 / Accepted: 30 March 2010 / Published online: 7 May 2010

Abstract
Introduction and hypothesis Intravesical botulinum toxin A (BTX-A) is emerging as a potential new treatment for refractory interstitial cystitis (IC). However, there has been conflicting evidence on this treatment's effectiveness. The aim of our systematic review was to assess the effectiveness and adverse effects of intravesical BTX-A in IC.
Methods Randomised controlled trials (RCTs) and prospective studies of relevance were identified, assessed for inclusion and then analysed by two independent reviewers.
Results Ten (three RCTs and seven prospective cohort) studies with a total of 260 participants were included. Eight studies reported improvement in symptoms. Urodynamic parameters were variable. Meta-analysis was not performed due to heterogeneity in reporting of outcomes. Some adverse events, e.g. dysuria and voiding difficulty, were noted (19 out of 260 were required to self-catheterise at anytime postoperatively).
Conclusions The evidence from the studies thus far suggests a trend towards short-term benefit with intravesical BTX-A injections in refractory IC, but further robust evidence should be awaited.

Keywords Botulinum toxin · Interstitial cystitis · Intravesical injection · Bladder pain syndrome

Abbreviations

BPS	Bladder pain syndrome
PBS	Painful bladder syndrome
IC	Interstitial cystitis
RCT	Randomised controlled trial
BFLUTS	Bristol Female Lower Urinary Tract Symptoms Questionnaire
GRA	Global Response Assessment
IIQ	Incontinence Impact Questionnaire
ICSI	Interstitial Cystitis Symptom Index
ICPI	Interstitial Cystitis Problem Index
KHQ	King's Health Questionnaire
QoL	Quality of life
IPPS	International Prostate Symptom Score
UDI	Urogenital Distress Inventory
VAS	Visual Analogue Score
MCC	Maximum cystometric capacity
FDV	First desire to void

S. Tirumuru (✉) · D. Al-Kurdi · P. Latthe
Birmingham Women's NHS Foundation Trust,
Metchley Park Road, Edgbaston,
Birmingham, UKB15 2TG
e-mail: drsahithi@rediffmail.com

Introduction

The European Society for the Study of Interstitial Cystitis/Painful Bladder Syndrome (ESSIC) uses the term bladder pain syndrome (BPS) instead of interstitial cystitis (IC) and/or painful bladder syndrome (PBS). ESSIC proposes that BPS would be diagnosed on the basis of chronic (>6 months) pelvic pain, pressure or discomfort perceived to be related to the urinary bladder accompanied by at least one other urinary symptom like persistent urge to void or frequency. Confusable diseases as the cause of the symptoms must be excluded. Further documentation and classification of BPS might be performed according to findings at cystoscopy with hydrodistension (HD) and morphological findings in bladder biopsies [1]. This is also supported by the Bladder Pain Committee of the International Consultation on Incontinence [2]. Formerly, the term IC was used for patients with 'typical cystoscopic and histological features'. The National Institute of Diabetes

and Digestive and Kidney Diseases (NIDDK) definition of IC requires objective findings of glomerulations or Hunner's ulcer at cystoscopy and subjective symptoms of bladder pain or urinary urgency and also includes multiple exclusion criteria such as age<18 years, duration of symptoms <9 months and absence of nocturia [3]. IC/BPS is far more common in women than in men. Of the estimated 1.3 million Americans with this syndrome, more than 1.2 million are women [4]. Median age of onset is 40 years and up to 50% of women experience spontaneous remissions unrelated to treatment, with a duration ranging from 1 to 80 months [5]. IC is a difficult condition to treat and, according to one study, 183 different therapies had been used [6]. The treatments include nonpharmacological measures such as dietary modification, lifestyle interventions/behavioural therapies, bladder training, peripheral transcutaneous nerve stimulation, pharmacological treatments such as oral medication, intravesical or bladder instillation therapy and surgical interventions like sacral neuromodulation and diversion. In recent years, intravesical injection of botulinum toxin A (BTX-A) has been explored as a new therapeutic option for BPS/IC. BTX-A is an extremely potent neurotoxin derived from the anaerobic bacterium *Clostridium botulinum* and acts by inhibiting the release of the neurotransmitter acetylcholine at the neuromuscular junction thereby decreasing muscle contractility at the injection site. The rationale for using BTX-A in BPS/IC is that it might have an antinociceptive effect on bladder afferent pathways [7]. We aimed to assess the effectiveness and safety of BTX-A in the treatment of IC/BPS by means of a systematic review.

Material and methods

Literature search

Studies for inclusion in the review were identified by searching the MEDLINE, EMBASE, CINAHL, CENTRAL (The Cochrane Library, Issue 2, 2009), MetaRegister of Controlled Trials and The National Library for Health from inception to June 2009 for relevant publications using relevant subject headings from each database. The following keywords were used for the search as text words without language restriction using The National Library for Health search 2.0 Healthcare Databases Advanced Search interface: 'botulinum toxin', 'botox', 'interstitial cystitis', 'dysport', 'pelvic pain' and 'painful bladder'. Two reviewers (ST and DA) independently assessed the titles and abstracts. The full paper was obtained if either reviewer considered the reference potentially relevant. Hand searches of the bibliographies and citation lists of all relevant reviews were also carried out to identify any missing studies not captured by electronic searches and potentially eligible studies were obtained as full reports. In addition, proceedings of the International Urogynecological Association and International Continence Society of the last 2 years were searched for abstracts as were the documents available on the website of the International Painful Bladder Foundation (June 2009).

Study selection

Randomised controlled trials (RCTs) or quasi-RCTs and prospective studies of participants who had intravesical BTX-A injections for BPS/IC with or without meeting the NIDDK criteria were included. Studies assessing the effect of BTX-A along with other interventions and/or studies assessing the effect of intravesical instillation with BTX-A in patients with BPS/IC were excluded. Two reviewers (ST and DA) assessed the eligibility of full papers against the review inclusion criteria, with disagreements resolved by discussion, if necessary, with a third reviewer (PL). In cases of duplication, the study which reported the most recent data results was included.

Data extraction

Two reviewers independently assessed methodological quality and extracted data on participants' characteristics, intervention, outcomes and adverse effects from the included studies using a purpose-designed proforma. All manuscripts meeting the selection criteria were assessed for their methodological quality. Quality was defined as the confidence that the study design, conduct and analysis minimised bias in the estimation of test accuracy. The Newcastle–Ottawa scale [8] was used to assess the quality of included nonrandomised studies and Jadad score for RCTs [9].

Types of participants

Participants in included studies were adult male and female patients with a clinical diagnosis of BPS/IC, with or without meeting the NIDDK criteria. Patients who had chemical or radiation cystitis were excluded.

Intervention

BTX-A injections injected submucosally into the bladder wall via cystoscope (rigid or flexible) under local anaesthesia (LA)/general anaesthesia (GA) with or without involving trigone.

Outcome measures

Most studies used clinical parameters such as frequency, nocturia and pain and different instruments such as the Bristol Female Lower Urinary Tract Symptoms Questionnaire (BFLUTS), Global Response Assessment (GRA),

Incontinence Impact Questionnaire (IIQ), Interstitial Cystitis Symptom Index (ICSI), Interstitial Cystitis Problem Index (ICPI), King's Health Questionnaire (KHQ), O'Leary–Sant Questionnaire, quality of life (QoL) from International Prostate Symptom Score (IPPS), Urogenital Distress Inventory (UDI) and Visual Analogue Score (VAS) to assess outcomes. Various urodynamic parameters such as maximum cystometric capacity (MCC), first desire to void (FDV), bladder compliance, first sensation of filling and detrusor pressure were assessed in most studies.

Results

Figure 1 summarises the flow for study selection in the systematic review. Initially, we identified 14 potential studies of which 10 were eligible for analysis [7, 10–18] and four out of these were published as abstracts [12–14, 16]. Four studies were excluded from the review as they did not meet the inclusion criteria [19–22] and one trial has just completed recruitment and the estimated study completion date is December 2010 [23]. The 10 studies that we analysed included three RCTs [11, 15, 16] and seven prospective nonrandomised studies [7, 10, 12–14, 17, 18]. Table 1 gives the details of patient characteristics, inclusion and exclusion criteria, intervention details and various outcomes including complications for nonrandomised prospective studies. Details of the patients, interventions, comparison and outcomes of RCTs are given in Table 2. There were a total of 260 participants (213 women and 18 men); one study with 29 patients did not report the sex of the participants [12]. The studies included patients between the ages of 18 and 83 years (mean age, 49.9 years). The included studies were uniformly small with sample sizes ranging from 10 to 67. Five studies used the NIDDK criteria for diagnosing IC [7, 11, 12, 15, 17], one study used clinical symptoms and presence of sterile urine to diagnose IC [18], whereas another study used clinical symptoms and cystoscopy to diagnose IC [10]. The criteria for diagnosing IC/BPS were not mentioned in three studies [13, 14, 16]. Preparation of BTX-A used was Botox (Allergan, Inc., Irvine, CA, USA) in five studies, Dysport (Ipsen Ltd., Slough, Berkshire, UK) in two studies [12, 16] and was not mentioned in two studies [15, 17]. In the two-centre case series [7], Dysport was used to treat Polish patients and Botox was used for US patients. The dose of BTX-A used

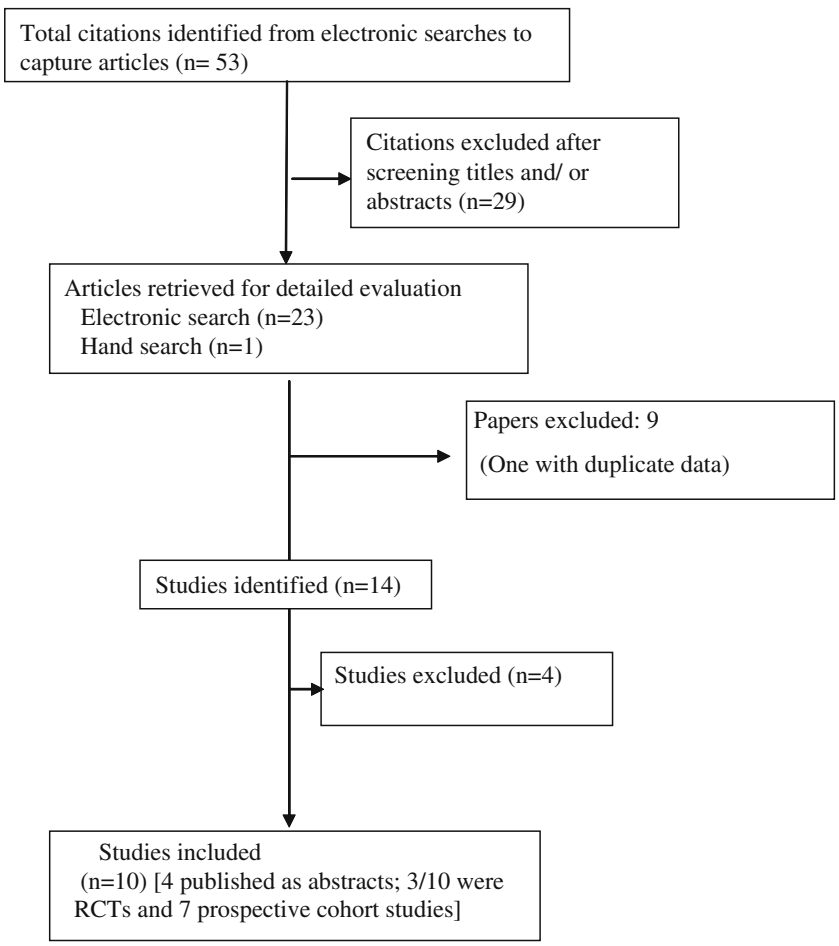

Fig. 1 Study selection process for systematic review of effectiveness and complications of BTX-A in BPS

Table 1 Characteristics of included nonrandomised prospective studies

No.	Primary author, publication date, location	Participants	Methods and duration of follow-up	Regimen—scheme	Outcome measures	Effectiveness	Complications
1	Ramsay K	11 female patients with IC (NIDDK criteria)	Prospective nonrandomised study	BTX-A dose : 200–300 IU	BFLUTS score, KHQ, 24 h frequency–volume chart and UDS performed preop and 6/52 post injection. Detrusor contractility was assessed using the modified PIP1	6 weeks:	2 patients had significant PVR necessitating CISC
	2007	Mean age 56 years (27–74)	Follow-up: 14 weeks	Injection site: suburothelium of the bladder, 20/30 different sites		Improvement in BFLUTS score, KHQ, urinary frequency p=0.07, NS (not significant) and p=0.57, respectively	
	Glasgow			Cystoscope : rigid		Two-part pain question of BFLUTS score and FDV were improved, p=0.009 and p=0.04, respectively	
				Needle: 23 G		10 weeks:	
				Anaesthesia: GA		BFLUTS score, p=0.03	
				Indwelling urethral catheter left overnight		KHQ p=0.03	
						Urinary frequency p=0.01	
						Two-part pain question of BFLUTS score p=0.009	
						14 weeks:	
						BFLUTS score and frequency were improved, p=0.01 and p=0.03, respectively	
						Slight improvement in MCC from 200 to 258 ml post-BTX-A (p=0.16)	
						5/11 women had complete sets of voiding data for pressure voiding at urodynamics before and after BTX-A injection. The contractility factor PIP1 was calculated for each void. The median increased from 39 to 46 NS (p=0.9)	
2	Giannantoni A	3 men and 12 women with PBS diagnosed based on clinical symptoms and sterile urine	Prospective nonrandomised study	BTX-A dose: 200 U (Allergan, Irvine, CA)	Voiding chart, VAS for pain and urodynamics pre and postop (1, 3, 5 and 12 months)	At 1 and 3 months:	Dysuria:
	2008	Mean age 58±9.9 years	Follow-up: 1 year	Injection site: submucosally in bladder lateral walls and trigone		13 (86.6%)reported subjective improvement	9 at 1 month, 4 at 3 months and 2 at 5 months

	Italy	Mean disease duration: 4.9±2.4 years		Cystoscope: rigid		Mean MCC improved from 256.4±33.5 to 361.7±48.4 and 352.5±50, respectively ($p<0.01$)	CISC:
				Needle: flexible		At 3 months:	3 at 24 h
				Anaesthesia: GA		Mean VAS score, day and night time frequency were decreased ($p<0.05$, <0.01 and <0.05, respectively)	2 at 3 months
				Indwelling urethral catheter left overnight		At 5 months:	1 at 5 months
						Bladder pain recurred in 11/15 patients.	Impaired detrusor contractility: 9 at 1 month
						Beneficial effects persisted in 26.6% of cases but increased VAS score and day and night time frequency compared to baseline were observed	
						At 12 months:	
						Pain recurred in all cases and clinical and urodynamic parameters same as baseline	
3	Hann-Chorng Kuo	8 women and 2 men with chronic IC based on characteristic symptoms and cystoscopy findings	Prospective study	BTX-A dose: Botox, 100–200 U (Allergan Co., USA)	3-day voiding diary, pain score using 5-point scoring system and urodynamics at baseline and 3 months after treatment. Pain score reported by patients as excellent (pain free), improved (pain score reduced by ≥2) or stationary (reduced by ≤1)	At 1 month:	In first 3 days after treatment, all had micturition pain, frequency, urgency exacerbation
	2005	Mean age: 47.2 years (28–73 years)	Follow-up: 3 months	Injection site: In 5 patients 100 U suburothelially into 20 sites on posterolateral bladder walls; Other 5 had additional 100 U injected into 5 sites of the trigone		2 reported improvement in bladder pain and urinary frequency	Mild difficulty in urination in first month reported in 7/10 and 4 had PVR >100 ml
	Taiwan	Mean disease duration: 7.5 years (3–12 years)		Cystoscope: rigid		At 3 months:	
				Needle: 22 G		Improvement was noted in cystometric bladder capacity, urinary frequency, MVV and pain score; $p=0.05$, $p=0.025$, $p=0.00$ and $p=0.003$, respectively	
				Anaesthesia: GA		No difference in first sensation of filling, detrusor pressure, bladder neck opening time, MFR, voiding efficiency, PVR (p=N.S.)	

Table 1 (continued)

No.	Primary author, publication date, location	Participants	Methods and duration of follow-up	Regimen—scheme	Outcome measures	Effectiveness	Complications
				Foleys catheter left for 1 day and oral antibiotics for 7 days		All patients found no change in quality of life after treatment Trigonal injection had no therapeutic effect on symptom or urodynamic improvement	
4	Smith	13 females diagnosed with IC according to NIDDK criteria	Two-centre case series	BTX-A dose: 100–200 U Dysport (Beaufour Ipsen) Polish patients or Botox (Allergan, US patients); a total of 10 to 20 U of BTX was used per injection site	US patients: O'Leary–Sant IC questionnaire (includes IC symptom Index and IC problem index voiding and pain indices)	Overall 8/12 (66.6%) noted improvement after BTX-A and symptom improvement lasted a mean of 3.72 months (range 1 to 8)	2 US patients treated with BTX-A injection noted decrease in force of urinary stream with some need to strain but no urinary retention
	2004	6 in the US (1 patient had intravesical instillation of BTX-A and we excluded the results of this patient from the review)	Follow-up: 1 and 3 months and three monthly thereafter	Injection site: submucosally in trigone and floor of the bladder	Polish patients: visual analogue pain scale, voiding charts	US patients	
	United States	7 in Poland		Cystoscope: rigid		Out of 5 patients who had intravesical injections, 1 was lost to follow-up. In 3/4 ICSI and ICPI mean scores improved by 71%($p<0.05$) and 69% ($p<0.05$) respectively and 1 did not respond	
	Poland	Mean patient age: 52.5±13.4 years Mean disease duration: 3.5±2.5 years		Needle: William's endoscopic needle Anaesthesia: GA or sedation		Polish patients Out of 7, 5 responded—daytime frequency and nocturia decreased by 44% and 45%, respectively, and VAS by 79% 1 month after treatment ($p<0.01$in all cases)	
				All procedures were day cases		FDV and MCC increased by 58% and 57%, respectively($p<0.01$)	
5	Stefan Carl	29 patients diagnosed with IC according to NIDDK criteria	Two-centre pilot study	BTX-A dose: 500 U Dysport® (Ipsen Pharma, Germany) diluted in 3 ml NaCl	Pre- and post-treatment urodynamics (6 weeks), VAS score and frequency/volume chart	83% (24/29) patients noted improvement of their symptoms after BTX-A treatment. MCC increased from 282 to 360 ml, bladder compliance from 13 to 23 ml/cm H_2O	2 had temporary haematuria

	2007		Follow-up: 6 months	Injection site: submucosally in the trigone and bladder floor into 20–25 sites		At 6 weeks:	3 had PVR of 100 ml
	Germany			Cystoscope: rigid		Daytime frequency, nocturia, urgency and pain by visual analogue scale decreased by 50%, 75%, 43% and 81%, respectively ($p<0.05$)	1 had urinary retention needing CISC
	Abstract only			Anaesthesia: GA or sedation		The improvement was maintained at 3 months	
						At 6 months:	
						Reinjection of BTX-A due to recurrence of pain was done in 7 patients (24%)	
6	Rui A. Pinto	16 females and 1 male with BPS included	Single centre prospective study	BTX-A dose: 100 U Botox	3-day voiding chart, O'Leary–Sant score, QoL from IPSS, pain visual analogue scale, a free flowmetry and pressure flow study were performed before treatment and 1, 3, 6 and 9 months later	At 1 and 3 months, respectively	No cases of voiding dysfunction or infection
	2009	Mean age: 48.1 years (26–81 years)	Follow-up: 9 months	Injection site: trigone only, 10 injections each containing 10 U in 10 ml of saline		MCC increased from 89±35 at baseline to 268±54 and 326±79 ml ($p<0.01$)	
	Portugal			Anaesthesia: GA		Urinary frequency decreased from 17±6.3 to 8.9±2.4 and 10±2.4 ($p<0.05$)	
	Abstract only					O'Leary–Sant score decreased from 15.3+12.8 (±3.2+3.4) to 9+4.39 (±0.8+2.4) and 6.2+4.3 (±1.3+1.4) ($p<0.05$)	
						QoL: 5.1 (±1.0) to 1.8 (±0.4) and 0.9 (±0.3) ($p<0.05$)	
						Bladder volume for the first episode of pain increased from 38±19 at baseline to 109±22 and 110±22.9 ml ($p<0.01$)	
						At 9 months, 7 patients requested another treatment	
7	A.M. Davies	IC group	Parallel prospective cohort study	BTX-A dose: 100–300 U of BOTOX (Allergan, Irvine, CA) diluted in 10 ml 0.9% saline per 100 U	Urodynamics and pre- and postoperative symptom scores comprising IIQ and the UDI-6	IC group: 1 patient (8%) had full relief of symptoms; further 3 experienced some improvement of frequency. Pain was generally unaltered by the treatment	3/13 patients had worsening of their pain
	2006	13 (12 female and 1 male)	Follow-up	Injection: multiple sites throughout the bladder, 0.5 ml per injection, sparing the trigone		Only 1/8 completing the pre- and postop UDI-6 score had a 2 point or better improvement in symptom score	3/13 needed CISC

Table 1 (continued)

No.	Primary author, publication date, location	Participants	Methods and duration of follow-up	Regimen—scheme	Outcome measures	Effectiveness	Complications
	UK	Criteria for diagnosis of IC not mentioned	Not-mentioned	Cystoscope: initially rigid, but latterly flexible cystoscope was used		IDO group: there was an 86% (11/13) treatment success rate. 4 patients required CISC, of which 2 considered treatment successful and 2 had no response. No patient had any worsening of symptoms; 9/11 patients completing a pre and post op UDI-6 had a 3 points or more improvement in symptom score	
	Abstract only	Mean age: 55 years (35–83 years) IDO group 13 patients Mean age 57 years (31–77 years)		Anaesthesia: Initial cases performed under GA, latterly under LA All procedures were day cases			

varied between the studies, sometimes changing within the study [17]. The amount of BTX-A injected was mostly 100–300 U (mostly at a concentration of 10 U/1 ml normal saline), except for two studies which used 500 U Dysport [12, 16]. In most studies, the number of injection sites in the bladder was between 20 and 30, except in two studies; in one, 10 injections were performed in the bladder trigone only [13] and, in the other study, injections in 40 sites in the posterior and lateral walls of the bladder were given [11]. Injection sites included trigone in four studies [10, 12, 15, 18] and trigone was spared in two studies [14, 16] and, in the remaining studies, it was not clearly mentioned whether trigone was injected or not. In most of the studies, BTX-A injections were done under general anaesthesia although some were done under sedation [7] or under local anaesthetic [14, 15]. Duration of follow-up varied between 3 and 24 months across studies. Only one study reported that seven out of 29 patients needed repeat injections because of recurrence of pain at 6 months [12].

Methodological quality of included studies

All except one study [14] had patients who were representative of this condition in the population (details in Table 1). The ascertainment of diagnosis, assessment of outcome and the instruments used to assess outcomes were satisfactorily described in all studies. The length of follow-up was described in six out of seven studies and, in four out of seven studies, <20% of patients were lost to follow-up (Table 3).

All RCTs were scored using a scale of 1 to 5 on the Jadad scale. One RCT [16] was of high quality (Jadad score of 5), the second one scored 3 on the Jadad scale [11] and the third one was of low methodological quality (Jadad score of 1) [15].

Effectiveness

Out of 10 studies, eight (including two RCTs) reported improvement in some or all of the following: frequency, pain, voided volume and QoL. The urodynamic parameters were variable. It is noteworthy that the two studies that reported no improvement with BTX-A used trigone-sparing technique [14, 16]. It was not feasible to perform meta-analysis as there was heterogeneity among the studies in definition of condition, design of the study, dose, method of intervention, outcome measures/assessment tools, length of follow-up, etc.

Adverse effects

The use of the regimen was generally well tolerated although mild adverse events such as dysuria, temporary

Table 2 Characteristics of included RCTs

No.	Author, publication date, location	Participants	Methods	Regimen—scheme	Outcome measures	Results	Tolerability
1	El-Bahnasy	36 women randomised	RCT of Bacillus	BTX-A	Initial evaluation:	Improvement in group 1 (BCG) vs. group 2 (BTX-A)	BTX-A group:
	2009	Outcome data for 32; NIDDK criteria met; symptoms for minimum of 6 months	Calmette–Guerin (BCG) (group 1) and BTX-A (group 2)	BTX-A dose: 300 U diluted in 30 ml of saline	History, examination, laboratory evaluation, radiological study including cystogram, filling cystometry and cystourethroscopy	Mean (SD) pre- treatment vs. post-treatment	3 had dysuria immediately after treatment, persisting for 3 to 4 weeks
	Egypt	Age 18 years or above	No ethical approval; informed consent obtained from patients	Injection sites: submucosally into 30 sites throughout the bladder including trigone	Final outcome evaluation:	Diurnal frequency:	1 had UTI
		Urinary frequency of 11 or more; 4 or higher score on a 0–9 Likert scale for pelvic pain	Follow-up:	Cystoscope: rigid; Needle: 25 G	1. Participants' GRA at the end of the study (symptoms rated on a 7-point scale compared with baseline). Successful responders defined as subjects with moderate or marked improvement on the GRA. 2. 24-h voiding diary parameters of diurnal and nocturnal frequency and pain, urgency, and dysuria recorded on a Likert scale from 0 to 9	Group 1: 16.6 (3.19) to 11.5 (2.3) (31%)	BCG group:
		Exclusion criteria: vesicoureteral reflux, immunocompromised, use of concomitant steroids/anticoagulant therapies, pregnancy	23 weeks for BCG group and 22 weeks for BTX-A group	Anaesthesia: LA	Data collected before and every 4 weeks after treatment	Group 2: 16.8 (2.6) to 5.2 (1.1) (68%)	5 had dysuria and 2 had UTI
			Participant dropouts during study:	All cases received perioperative oral antibiotics BCG group		Nocturnal frequency: Group 1: 6.0 (6.0) to 2.7 (1.07) (54%)	1 case stopped treatment because of severe haemorrhagic cystitis
			Group 1: 1 drop out due to severe haemorrhagic cystitis	Weekly intravesical BCG instillations of 5×10^8 colony-forming units for 6 weeks		Group 2: 6.3 (1.8) to 0.27 (0.47) (100%)	
			Group 2: 2 patients lost to follow-up and 1 patient diagnosed with TCC			Pelvic pain:	
			Allocation concealment: not stated			Group 1: 5.4 (1.26) to 1.05 (0.77) (81%)	

Table 2 (continued)

No.	Author, publication date, location	Participants	Methods	Regimen—scheme	Outcome measures	Results	Tolerability
			Randomisation: Alternate sequence Blinding: not used Power calculation: not stated ITT analysis—not done			Group 2: 5.8 (1.39) to 0.2 (0.4) (96%) Urgency: Group 1: 6.38 (1.3) to 1.83 (1.02) (71%) Group 2: 6.4 (1.03) to 0.05 (0.25) (100%) Dysuria: Group 1: 4.8 (1.4) to 0.8 (0.7) (82%) vs. Group 2: 4.8 (1.2) to 0.38 (0.5) (92%) The global interstitial cystitis survey improvement 71% vs. 92% 11/16 (68.75%) patients in group I vs. 14/16 (87.50%) in group II continued to have an excellent response in all parameters measured The patients in group II showed a statistically significant improvement in all parameters compared to group I	
2	JA Manning 2009	49 female patient invited; results available for 41 patients at 3 months (20 Dysport vs. 21 placebo) Inclusion criteria:	Randomised double blind study of effectiveness of botulinum A toxin for treatment of refractory PBS Consent obtained from patients; investigator initiated; work supported by industry	Treatment group: BTX-A: 500 U	Outcome measures: Baseline urodynamics, O'Leary–Sant, urge IIQ scores, maximum and average functional capacity, day and night frequency recorded just prior and at 1 week, 6 weeks, 3, 6 and 12 months post-treatment	At 3 months O'Leary–Sant results:	PVR>200 ml in 2 patients

Australia	Women with refractory PBS	Follow-up: 1 year	Dysport diluted in 30 ml saline	A free urinary flow rate with PVR performed 1 week post-treatment	Significant improvement in both groups (p=0.001). Interaction between Dysport vs. placebo and time NS for O'Leary–Sant PI (p=0.06) and for O'Leary–Sant SI (p=0.48)
Abstract only	Exclusion criteria:	Allocation concealment:	cystodistension with Dysport injected submucosally at approx. 30 sites in 1 ml aliquots, sparing trigone		Urge IIQ score and daytime frequency:
	None mentioned	Pharmacy controlled	Needle: 30 cm Bard 23 G		Both groups improved, p=0.025 and p=0.002, respectively
	Average age 54 years (20–77 years)	Randomisation:	Anaesthesia: GA		Interaction between time and treatment allocation NS, p=0.29 and p=0.38, respectively
		Computer generated	Control group: cystodistension (4 min) plus injection of 30 ml of saline		For nocturia and MBC there was no effect over time, p=0.38 and p=0.52, respectively
		Blinding: double blinded	Bladder biopsy was taken if not already available		Interaction between time and treatment allocation NS, p=0.52 and p=0.39, respectively
		Power calculation: done	Subjects with no satisfactory improvement at 3 months follow-up were permitted access to active treatment		Biopsy data did not show correlation between those with inflammatory changes consistent with the diagnosis and treatment effect
		ITT analysis: yes			Results could not be compared meaningfully after 3 months for the whole group as at 3 months, 29 subjects with unsatisfactory response opted to have Dysport

Table 2 (continued)

No.	Author, publication date, location	Participants	Methods	Regimen—scheme	Outcome measures	Results	Tolerability
3	Hann-Chorng Kuo	n=70 randomised	RCT to compare effectiveness of BTX-A injections followed by HD with HD alone	Treatment group:	3-day voiding diary, O'Leary–Sant IC questionnaire (ICSI and ICPI), VAS for pain, GRA and UDS at baseline and 3/12 post-HD	GRA improvement at 3 months:	BTX-A 200 U group vs. BTX-A 100 U group
	2009	67 patients analysed (56 women and 11 men)	Study approved by institutional review board and university ethics committee	BTX-A dose: 200 or 100 U Botox (Allergan, Irvine, CA)	Primary end-point was assessment at 3/12 after HD and follow-up at 3-month intervals until recurrence of symptoms	BTX-A 200 U group 12/15	UTI: 3 vs. 0
	Taiwan	BTX-A group: 44 (15 patients 200 U; 29 patients 100 U)	Informed consent obtained from patients	Injection site: suburothelially at 40 sites in posterolateral bladder walls. 5 and 2.5 U in 0.5 ml per site in 200 and 100 U BTX-A groups, respectively	Patients with moderate and marked improvement on a 7-point GRA scale were considered to have successful treatment outcome	BTX-A 100 U group 21/29 (72%)	Haematuria: 2 vs. 0
		Control group(HD): 23	BTX-A group: 200 or 100 U BTX-A followed by cystoscopic HD 2 weeks later	Cystoscope: rigid		HD group 11/23 (48%)	Dysuria: 7 vs. 3
		Dropouts: 3	Control group received identical HD without BTX-A injections	Needle: 23 G		(p=0.032)	1 in HD group
		NIDDK criteria met	9/15 patients in BTX-A 200 U group developed complications and the study protocol was changed at 1 year and 6 patients were reassigned to BTX-A 100 U group	Anaesthesia: GA		Mean MBC (SD) improvement during HD 2 weeks later:	Large PVR: 5 vs. 2
		All patients had been treated with conservative treatments for ≥6 months without response	All patients remained on pentosan polysulphate throughout the study	14 F urethral catheter placed for 1 day and oral antibiotics for 7 days		BTX-A 200 U group:	Acute urinary retention: 2 vs. 1

Mean duration (SD, range) of IC/PBS: 8 years (2–5, 5–15 years)	Follow-up: 2 years	Cystoscopic HD was performed under GA 2 weeks after BTX-A injection to an intravesical pressure of 80 cm H_2O for 15 min	21% from 589 (182) to 714 (175) (p=0.001)	Chronic urinary retention: 2 vs. 0
Mean age (SD, range)	Allocation concealment: done	Control group: cystoscopic HD using similar methods as in BTX-A group	BTX-A 100 U group:	
200 U group: 45.7 years (12.5, 26–68 years)	Randomisation: permuted block		24% from 646 (196) to 802 (228) (p<0.001)	
100 U group: 47.7 years (14.7, 26–84 years)	Blinding: not used		(p=0.703)	
HD group: 52.5 years (15.3, 30–83 years)	Power calculation: done		Improvement in ICSI and IPSI at 3 months:	
	ITT analysis: yes		BTX-A 200 U group:	
			ICSI: 13.9 (2.53) to 8.9 (5.58)	
			ICPI: 12.3 (1.40) to 7.13 (4.52)	
			BTX-A 100 U group:	
			ICSI: 12.5 (2.15) to 8.17 (4.06)	
			ICPI: 11.1 (2.05) to 6.93 (3.58)	
			HD group:	
			ICSI: 12.8 (3.41) to 9.87 (4.85)	
			ICPI: 11.1 (2.60) to 8.57 (4.59)	
			Significant decrease in all 3 groups but changes among them NS	
			Pain VAS score and FBC improvement at 3 months:	
			Pain VAS score decreased by 55%, 39% and 18% (p= 0.007)	
			FBC increased by 68%, 17% and 9 % (p=0.05) in BTX-A 200 U group, BTX-A 100 U group and HD group, respectively	

Table 2 (continued)

No.	Author, publication date, location	Participants	Methods	Regimen—scheme	Outcome measures	Results	Tolerability
						Success rate in BTX-A 200 U, BTX-A 100 U and HD groups: At 6 months: 11/15, 20/29 (69%) and 8/23 (35%) At 12 months: 11/15, 13/29 (45%) and 6/23 (26%), respectively At 18 months: successful result sustained by 9/15, 12/29 (41%) and 5/23 (22%) At 24 months: successful result sustained by 7/15, 6/29 (21%) and 4/23 (17%), respectively (p=0.007)	

BCG Bacillus–Calmette–Guerin, *BFLUTS* Bristol Female Lower Urinary Tract Symptoms Questionnaire, *BPS* bladder pain syndrome, *FDV* first desire to void, *FBC* functional bladder capacity, *F/U* follow-up, *GRA* Global Response Assessment, *ICSI* Interstitial Cystitis Symptom Index, *ICPI* Interstitial Cystitis Problem Index, *IDO* idiopathic detrusor overactivity, *IIQ* Incontinence Impact Questionnaire, *IPSS* International Prostate Symptom Score, *ITT* intention to treat analysis, *KHQ* King's Health Questionnaire, *LA* local anaesthesia, *UDS* urodynamics, *PVR* post-void residual, *CISC* clean intermittent self-catheterisation, *MFR* maximum flow rate, *MVV* maximum voided volume, *MBC* maximum bladder capacity, *MCC* maximum cystometric capacity, *PIP*, projected isovolumetric pressure, *RCT* randomised control trial, *NS* not significant, *PBS* painful bladder syndrome, *VAS* Visual Analogue Score, *QoL* quality of life, *TCC* transitional cell carcinoma, *U* units, *UDI* Urogenital Distress Inventory

Table 3 Quality of nonrandomised studies included in the systematic review of effectiveness of botulinum toxin therapy in IC

Name of the study	Selection	Ascertainment of diagnosis	Assessment of outcome	Instrument for assessment of outcome	Follow-up long enough	Adequacy of follow-up
Ramsay	Truly representative of population[a]	NIDDK[a]	Objective and subjective self-report[a]	Validated (BFLUTS, KHQ, FV chart)[a]	Yes[a]	Complete[a]
Giannantoni	Truly representative of population[a]	Clinical symptoms[a]	Self-report and objective assessment[a]	Validated (VAS, voiding chart, urodynamics)[a]	Yes[a]	Complete[a]
Hann-Chorng Kuo	Truly representative of population[a]	Clinical symptoms and cystoscopy[a]	Self-report and objective assessment (UDS)[a]	5-point scoring system (not validated), urodynamics and voiding charts[a]	Yes[a]	Complete[a]
Smith	Truly representative of population[a]	NIDDK[a]	Self-report and urodynamics[a]	Validated O'Leary–Sant, VAS and voiding diary and urodynamics[a]	Yes[a]	1/13 lost to follow-up[a]
Stefan C.	Truly representative of population[a]	NIDDK[a]	Self-report and urodynamics[a]	VAS, frequency volume chart and urodynamics[a]	Yes[a]	No description
Davies	No description	Clinical symptoms[a]	Self-report and urodynamics in some[a]	IIQ and UDI-6[a]	Not mentioned	No description
Pinto R. Pinto	Truly representative of population	Clinical symptoms[a]	Self-report and urodynamics[a]	Validated (O'Leary–Sant pain VAS, voiding chart, QoL from IPSS urodynamics)[a]	Yes[a]	Complete[a]

[a] Fulfilled the quality assessment per Ottawa–Newcastle scale

haematuria, urinary tract infection (UTI), voiding difficulty with need for clean intermittent self-catheterisation (CISC), impaired detrusor contractility and decrease in force of urinary stream were reported. In this systematic review, 19 out of 260 patients who had BTX-A needed to perform CISC (seven patients had post-void residual [PVR] >100 ml and two patients had PVR >200 ml) at any time postoperatively. Thirty-five patients complained of dysuria or pain exacerbation after treatment and 18 out of 260 had impaired detrusor contractility or mild difficulty in urination but were able to empty bladder completely with straining. Four patients developed temporary haematuria and four patients had UTI following the procedure.

Discussion

The limited evidence from the included studies suggests that intravesical BTX-A injections may be the appropriate therapy for patients with refractory IC and there is a trend towards benefit. To the best of our knowledge, this systematic review, with the data that was utilised, summarises all the prospective nonrandomised studies and RCTs that exist on this topic.

There are several strengths of this review. The review addressed a clear question. The search was thorough and systematic without language restrictions. Two reviewers independently did the study selection and data extraction to minimise errors. We attempted to contact authors of published and unpublished studies to obtain further details.

The trials were of small sizes with short-term follow-up. We could not get more details on some of the abstracts in spite of attempting to contact the authors. Analysing the efficacy of BTX-A injections in the treatment of IC/BPS is challenging because of the heterogeneity of the definition of BPS, different methods and doses of injection of Botox, varied number of outcome measures employed and small number of participants. Hence, firm conclusions cannot be drawn about the effectiveness of intravesical BTX-A injection in the treatment of BPS.

Intravesical BTX-A may be advantageous in selected patients with refractory BPS who have failed to respond to conventional treatments. However, we agree that it should be ideally used in clinical trial setting [24] pending further evidence. The review has shown the clear need for further randomised trials that are methodologically sound and sufficiently powered with adequate follow-up. Furthermore, study design should include assessing the optimum dose and sites of BTX-A injection and duration of efficacy. Better concordance or uniformity between studies in terms of defining the condition and use of instruments measuring quality of life will aid in future interpretation of data and clinical application.

Acknowledgements Derick Yates, medical librarian at BWHFT, did the literature search for us.

Conflicts of interest None.

References

1. Van de Merwe JP, Nordling J, Bouchelouche P, Bouchelouche K, Cervigni M, Daha LK et al (2008) Diagnostic criteria, classification, and nomenclature for painful bladder syndrome/interstitial cystitis: an ESSIC proposal. Eur Urol 53(1):60–67
2. Hanno P, Lin A, Nordling J, Nyberg L, van Ophoven A, Ueda T et al (2010) Bladder pain syndrome committee of the international consultation on incontinence. Neurourol Urodyn 29(1):191–198
3. Gillenwater JY, Wein AJ (1988) Summary of the National Institute of Arthritis, Diabetes, Digestive and Kidney Diseases Workshop on Interstitial Cystitis, National Institutes of Health, Bethesda, Maryland, August 28–29, 1987. J Urol 140:203–206
4. Clemens JQ, Link CL, Eggers PW, Kusek JW, Nyberg LM Jr, McKinlay JB (2007) Prevalence of painful bladder symptoms and effect on quality of life in black, Hispanic and white men and women. J Urol 177:1390–1394
5. Held PJ, Hanno PM, Wein AJ, Pauly MV, Cahn MA (1990) Epidemiology of interstitial cystitis. In: Hanno PM, Staskin DR, Krane RJ, Wein AJ (eds) Interstitial cystitis. Springer, London, pp 29–48
6. Rovner E, Propert KJ, Brensinger C, Wein AJ, Foy M, Kirkemo A et al (2000) Treatments used in women with interstitial cystitis: the interstitial cystitis data base (ICDB) study experience. The Interstitial Cystitis Data Base Study Group. Urology 56:940–945
7. Smith CP, Radziszewski P, Borkowski A, Somogyi GT, Boone TB, Chancellor MB (2004) Botulinum toxin A has antinociceptive effects in treating Interstitial cystitis. Urology 64:871–875
8. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al (2000) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Proceedings of the Third Symposium on Systematic Reviews: Behind the Basics, Oxford, England, 4–9 July (Ref Type: Electronic Citation)
9. Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ et al (1996) Assessing the quality of reports of randomized clinical trials: is blinding necessary? Control Clin Trials 17:1–12
10. Kuo HC (2005) Preliminary results of suburothelial injection of botulinum a toxin in the treatment of chronic interstitial cystitis. Urol Int 75:170–174
11. Kuo HC, Chancellor MB (2009) Comparison of intravesical botulinum toxin type A injections plus hydrodistention with hydrodistention alone for the treatment of refractory interstitial cystitis/painful bladder syndrome. BJU Int 104:657–661
12. Carl S, Grosse J, Laschke S (2007) Treatment of interstitial cystitis with botulinum toxin type A. Eur Urol 6:248
13. Pinto RA, Silva A, Lopes T et al (2009) Intra-trigonal injection of botulinum toxin A in patients with bladder pain syndrome-results at 9 months follow up. J Urol 181(4, supplement):20, Ref Type: Abstract
14. Davies A, Chahal R, Inman R, Urwin G (2006) Intravesical botulinum A toxin (Botox)—does it have a role in the management of interstitial cystitis. Eur Urol Suppl 5(supplements 2):22, Ref Type: Abstract
15. El-Bahnasy A, Farahat YA, El-Bendary M, Taha MR, El-Damhogy M, Sherif Mourad (2009) A randomized controlled trial of bacillus Calmette–Guerin and botulinum toxin-A for the treatment of refractory interstitial cystitis. UroToday International Journal 2. doi:10.3834/uij.1944-5784.2008.12.06 (Ref Type: Electronic Citation)
16. Manning JA, Dwyer P, Rosamilia A, Murrary C, Thomas E, Beattie K (2009) Prospective randomised double blind study of the effectiveness of botulinum A toxin for treatment of refractory painful bladder syndrome. Int Urogynecol J Pelvic Floor Dysfunct 20(suppl 2):S87–S88, Ref Type: Abstract
17. Ramsay AK, Small DR, Conn IG (2007) Intravesical botulinum toxin type A in chronic interstitial cystitis: results of a pilot study. Surgeon 5:331–333
18. Giannantoni A, Porena M, Costantini E, Zucchi A, Mearini L, Mearini E (2008) Botulinum A toxin intravesical injection in patients with painful bladder syndrome: 1-year followup. J Urol 179:1031–1034
19. Giannantoni A, Costantini E, De Stasi S, Mearini E, Santaniello F, Vianello A et al (2007) Intravesical passive delivery of botulinum A toxin in patients affected by painful bladder syndrome: a pilot study. Eur Urol 6(supplements 2):246, Ref Type: Abstract
20. Liu HT, Kuo HC (2007) Intravesical botulinum toxin A injections plus hydrodistension can reduce nerve growth factor production and control bladder pain in interstitial cystitis. Urology 70:463–468
21. Chuang YC, Kim DK, Chiang PH, Chancellor MB (2008) Bladder botulinum toxin A injection can benefit patients with radiation and chemical cystitis. BJU Int 102:704–706
22. Tara Frenkl L, Raymond R (2005) Injectable neuromodulatory agents: botulinum toxin therapy. Urol Clin N Am 32:89–99
23. Miller JL (2009) Botox as a treatment for interstitial cystitis in women: a randomized placebo controlled trial. University of Washington, Seattle (Ref Type: Electronic Citation)
24. Hanno P, Dmochowski R (2009) Status of international consensus on interstitial cystitis/bladder pain syndrome/painful bladder syndrome: 2008 snapshot. Neurourol Urodyn 28(4):274–286, Ref Type: Abstract