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META-ANALYSIS

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Intravesical Botulinum Toxin A Injections for Bladder Pain Syndrome/Interstitial Cystitis: A Systematic Review and Meta-Analysis of Controlled Studies

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The role of intravesical botulinum toxin A (BTX-A) injections in bladder pain syndrome/interstitial cystitis (BPS/IC) has not been clearly defined. The aim of this study was to evaluate high-level evidence regarding the efficacy and safety of BTX-A injections for BPS/IC.

Material/Methods: We conducted a comprehensive search of PubMed, Embase, and Web of Science, and conducted a systematic review and meta-analysis of all available randomized controlled trials (RCTs) and controlled studies assessing BTX-A injections for BPS/IC.

Results: Seven RCTs and 1 retrospective study were identified based on the selection criteria. Pooled analyses showed that although BTX-A was associated with a slightly larger volume of post-void residual urine (PVR) (weighted mean difference [WMD] 10.94 mL; 95% confidence intervals [CI] 3.32 to 18.56; p=0.005), patients in this group might benefit from greater reduction in pelvic pain (WMD –1.73; 95% CI –3.16 to –0.29; p=0.02), Interstitial Cystitis Problem Index (ICPI) scores (WMD –1.25; 95% CI –2.20 to –0.30; p=0.01), and Interstitial Cystitis Symptom Index (ICSI) scores (WMD –1.16; 95% CI –2.22 to –0.11; p=0.03), and significant improvement in daytime frequency of urination (WMD –2.36; 95% CI –4.23 to –0.49; p=0.01) and maximum cystometric capacity (MCC) (WMD 50.49 mL; 95% CI 25.27 to 75.71; p<0.00001). Nocturia, maximal urinary flow rate, dysuria, and urinary tract infection did not differ significantly between the 2 groups.

Conclusions: Intravesical BTX-A injections might offer significant improvement in bladder pain symptoms, daytime urination frequency, and MCC for patients with refractory BPS/IC, with a slightly larger PVR. Further well-designed, large-scale RCTs are required to confirm the findings of this analysis.

MeSH Keywords: **Administration, Intravesical • Botulinum Toxins, Type A • Chronic Pain • Cystitis, Interstitial**

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Background

Bladder pain syndrome (BPS) is a chronic disease that has a dramatically negative influence on patients' emotions, sexual and other behaviors, and cognitive abilities. The typical symptom of BPS is persistent or recurrent pelvic pain connected with bladder filling, associated with increased voiding frequency, without the existence of urinary tract infection (UTI) or other recognizable pathology [1]. The European Society for the Study of Interstitial Cystitis suggested the term BPS to encompass all patients with bladder pain, and defines interstitial cystitis (IC) with typical Hunner's lesions as BPS type 3C [1]. A recent report demonstrated BPS/IC may be more common than previously thought, with a prevalence between 2.70% and 6.53% in women in the United States [2]. In addition, it was estimated that BPS/IC was responsible for $750 million in direct costs per year in the United States alone [3].

As the pathogenesis of BPS/IC is still in dispute, there is no standard management for this disease. There are more than 180 treatment approaches reported for BPS/IC, but therapeutic results are usually disappointing [4]. Treatment protocols are currently aimed at alleviating pelvic pain, as pain is thought to induce other symptoms, such as increased daytime voiding frequency and nocturia [1,5].

Botulinum toxin A (BTX-A) has antinociceptive properties, and was first suggested as a treatment for refractory BPS/IC in 2004. BTX-A injections have been widely used for the management of conditions associated with pain and other lower urinary tract disorders, such as overactive bladder, neurogenic detrusor overactivity, idiopathic detrusor overactivity, and bladder outflow obstruction [6,7]. Owing to increasing evidence supporting its effectiveness and safety in urologic use, BTX-A has been licensed for the treatment of overactive bladder and neurogenic detrusor overactivity. The exact mechanism of the antinociceptive effect of BTX-A is not yet known. BTX-A may alleviate pain by inhibiting the release of several sensory neurotransmitters involved in bladder afferent pathways [8].

A previous systematic review reported the benefit of BTX-A injections in BPS/IC [9]. Unfortunately, most of the studies included in that systematic review were non-controlled trials, which might have affected the validity of the conclusion. Recently, several randomized controlled trials (RCTs) examining the effect of BTX-A injections have been published, but the results were conflicting [10–16]. Therefore, we systematically searched and analyzed all available literature to critically assess the efficacy and safety of BTX-A injections in the treatment of BPS/IC.

Material and Methods

Evidence acquisition

According to the Preferred Reporting Items for Systematic reviews and Meta-Analyses guidelines and the Quality of Reporting of Meta-analyses of Randomized Controlled Trials statement, we developed a pre-specified protocol of objectives, literature search strategies, eligibility criteria, data extraction, quality assessment, and methods of statistical analysis.

Literature-search strategy

A literature search of the electronic databases PubMed, Embase, and Web of Science was performed in October 2015 without restrictions for regions, publication types, or languages. We used the medical subject headings: botulinum toxins, type A, and the search terms botulinum toxin, botulinum neurotoxin, onabotulinumtoxinA, incobotulinumtoxinA, Xeomin, abobotulinumtoxinA, BTX, Botox, Dysport, Prosigne, PurTox, and Xeomin, associated with the search terms interstitial cystitis, bladder pain syndrome, and painful bladder syndrome. The reference lists of all identified studies and previous systematic reviews were screened for other potentially relevant articles.

Inclusion and exclusion criteria

All available controlled studies that assessed effectiveness of BTX-A injections in patients diagnosed with IC/BPS were eligible. Studies that did not have a comparator (no BTX-A injections) were excluded. Duplicate reports, editorials, animal models, and case reports were also excluded.

Data extraction and outcomes of interest

Two authors (J. P. Wang and Q. Wang) independently extracted data from the included studies, including study characteristics (diagnostic criteria, inclusion and exclusion criteria, and follow-up), dose of BTX-A injections, characteristics of participants (age and sex), and endpoints (primary endpoints, secondary endpoints, and adverse events). Any disagreements regarding extracted data were settled by the senior author (P. Wu).

The primary endpoints used in the included studies were the 0-10 Visual Analog Scale (VAS), the Interstitial Cystitis Problem Index (ICPI), and the Interstitial Cystitis Symptom Index (ICSI). The secondary endpoints included daytime frequency, nocturia, maximum cystometric capacity (MCC), and maximal urinary flow rate (Qmax). The main adverse events of BTX-A injections were increased post-void residual urine (PVR), dysuria, and UTI.

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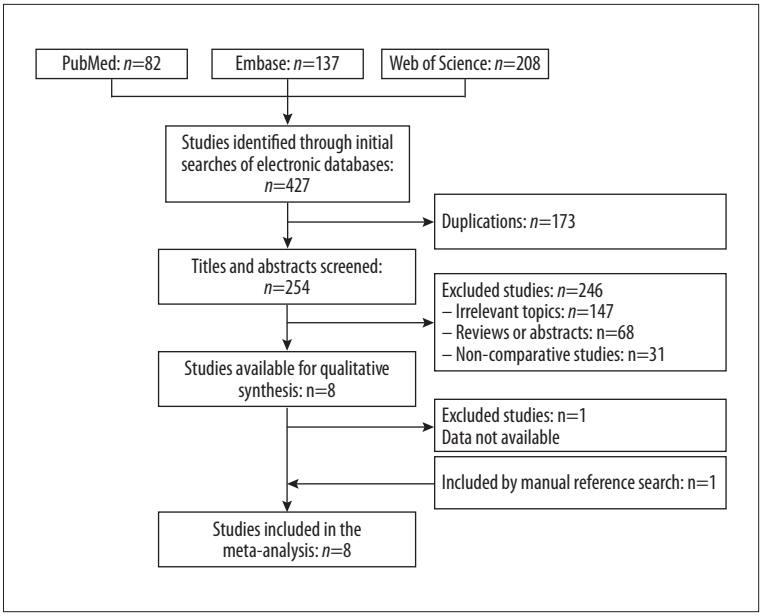

Figure 1. Flow diagram of trials included and excluded.

Assessment of risk of bias and statistical analysis

We assessed risk of bias in the included RCTs using the Cochrane risk of bias assessment tool, and performed the meta-analysis using Review Manager software version 5.2 (Cochrane Collaboration, Oxford, UK). The quality of retrieved retrospective studies was assessed using the modified Newcastle-Ottawa scale [17]. Authors were contacted for methodological details if they were not adequately reported in the articles.

The recorded changes were subtracted from baseline to eliminate the influence of baseline symptoms. For studies that did not provide the data as change from baseline, the mean and deviation of the endpoint were used. Weighted mean difference (WMD) and relative risk (RR) were used for continuous and dichotomous outcomes, respectively, and 95% confidence intervals (CIs) were applied for all results.

Heterogeneity between studies was assessed by the chi-square test and quantified by the I^2 statistic. A p value <0.10 or an I^2>50% indicated the existence of substantial heterogeneity across studies. The fixed-effects model was used if there was no significant heterogeneity; otherwise, the random-effects model was used. For RCTs with 3 groups, we made relevant pairwise comparisons. Potential publication bias was assessed with funnel plots.

Results

Search results

The initial search produced 427 articles. One additional article was identified through examination of reference lists of primary conference abstracts and previous reviews [15]. Of these studies, 7 RCTs and 1 retrospective study met the inclusion criteria and were included in the final meta-analysis (Figure 1).

Description of eligible studies

The main characteristics of the eligible studies are summarized in Table 1. Participants with BPS/IC were diagnosed based on the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) criteria [10,13–16], or on clinical presentation and cystoscopic findings [11]. All trials aimed to assess the efficacy of intravesical BTX-A injections for the treatment of BPS/IC. The BTX-A dose was between 100 U and 500 U. The participants were predominantly female (94%, 400 of 427), and patients in 5 RCTs and the retrospective study had undergone unsuccessful conventional treatments [10,14–16,18,19]. The average follow-up time was 2.6 months (range, 1–5.75 months).

Methodological Quality and publication bias

The overall methodological quality of included studies was moderate. Risk of bias assessment indicated that 1 RCT had a low risk of bias [16], 5 RCTs had a moderate risk of bias [10,11,14,15,19], and 1 RCT had a relatively high risk of bias [13] (Supplementary Figure 1). The representativeness of patients, comparability of the study groups, and assessment of outcome were satisfactorily described in the retrospective study [18] (Supplementary Table 1). The funnel plots were largely symmetric (Supplementary Figure 2), indicating no obvious publication bias in this meta-analysis.

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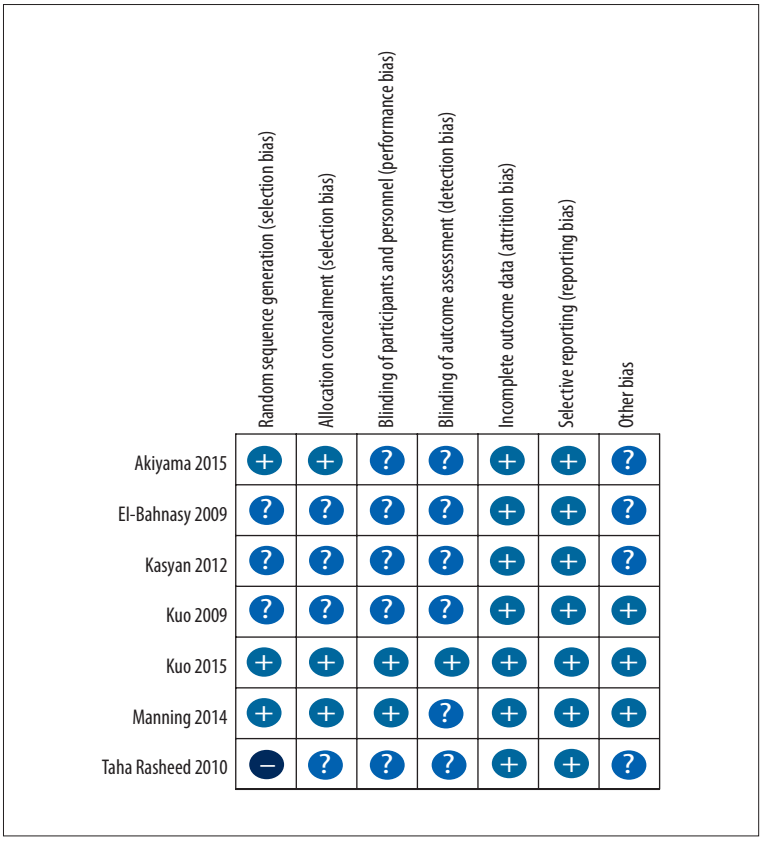
Table 1. Characteristics of eligible studies.

Study	Diagnostic criteria	Design	LE	BTX-A dose	Patients, no.		Mean age, yr	Women, %	Follow-up, mo
					BTX-A	Control			
Kuo 2015	NIDDK	RCT	1	100 U	40	20	50.8	86	2
Kasyan 2012	Clinical and cystoscopic	RCT	2	100 U	15	17	NA	100	3
Manning 2014	NIDDK	RCT	1	500 U	25	25	53.5	100	3
Kuo 2009	NIDDK	RCT	1	100 U	29	23	48.9	83	3
				200 U	15	23	48.9	83	3
El-Bahnasy 2009	NIDDK	RCT	2	300 U	16	16	NA	100	5.5 *vs.* 5.75
Taha Rasheed 2010	NIDDK	RCT	2	300 U	14	14	NA	100	4.75 *vs.* 5.25
Akiyama 2015	NIDDK	RCT	1	100 U	18	16	64.9	76	1
Gao 2015	NIDDK	R	3	100 U	66	58	NA	100	1

BTX-A – botulinum toxin A; NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases; NA – not applicable; RCT – randomized controlled trail; R – retrospective; LE – level of evidence.



Supplementary Figure 1. Risk of bias in randomized controlled trials included in this meta-analysis.

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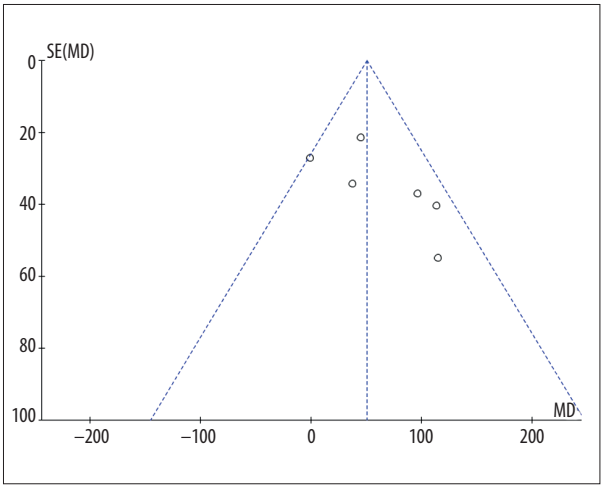
Supplementary Table 1. Risk of bias in retrospective studies using modified Newcastle-Ottawa scale.

Study	Selection			Comparability	Outcome	
	Representative treatment group	Representative control group	Ascertainment of diagnosis		Assessment of outcome	Adequate follow-up
Gao 2015	Yes	Yes	NIDDK*	Comparable for baseline symptom scores**, urinary frequency, age, and gender	Yes	Yes

* NIDDK – National Institute of Diabetes and Digestive and Kidney Diseases; ** Symptom scores included O'Leary-Saint score, the 0–10 Visual Analog Scale score, and quality of life score.



Supplementary Figure 2. Funnel plots of maximum cystometric capacity.

Primary outcomes

Pelvic pain

Five trials assessed pelvic pain using the VAS [11,14,16,18,19].

Pooled analysis showed that the BTX-A group was associated with a significant reduction in VAS score compared with the control group (WMD –1.73; 95% CI –3.16 to –0.29; p=0.02) (Figure 2). Two RCTs using the 0–9 Likert scale to assess pelvic pain indicated that BTX-A was linked with a significant reduction in pelvic pain versus controls [13,15].

Interstitial Cystitis Problem Index and Interstitial Cystitis Symptom Index

Five RCTs reported ICPI and ICSI scores [10,11,14,16,19]. Pooled analysis showed significant reduction in ICPI scores (WMD –1.25; 95% CI –2.20 to –0.30; p=0.01; Figure 3) and ICSI scores (WMD –1.16; 95% CI –2.22 to –0.11; p=0.03; Figure 4).

Secondary outcomes

Daytime frequency and nocturia

All RCTs except for 1 assessed daytime frequency and nocturia [11]. Pooled analysis detected a significant difference in daytime frequency (WMD -2.36; 95% CI –4.23 to –0.49; p=0.01;

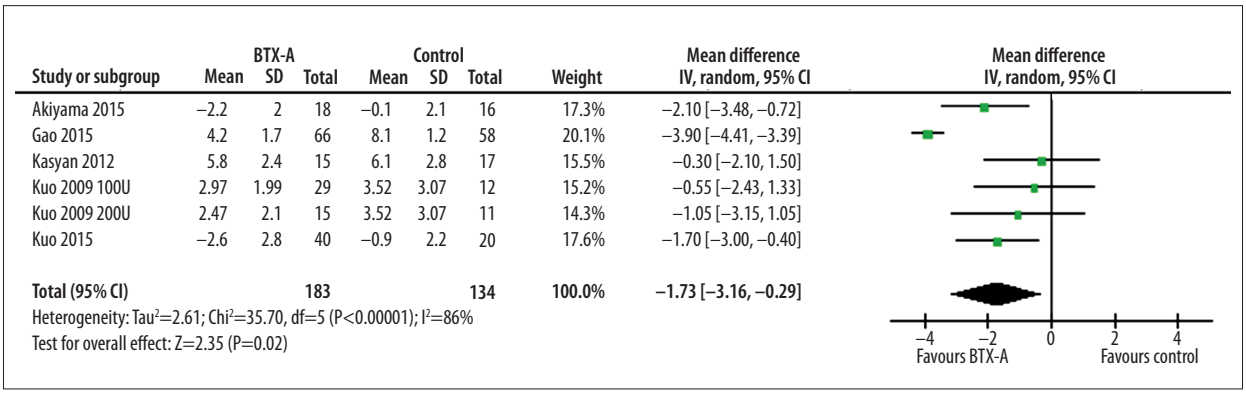


Figure 2. Forest plot of pelvic pain measured by visual analog scale score.

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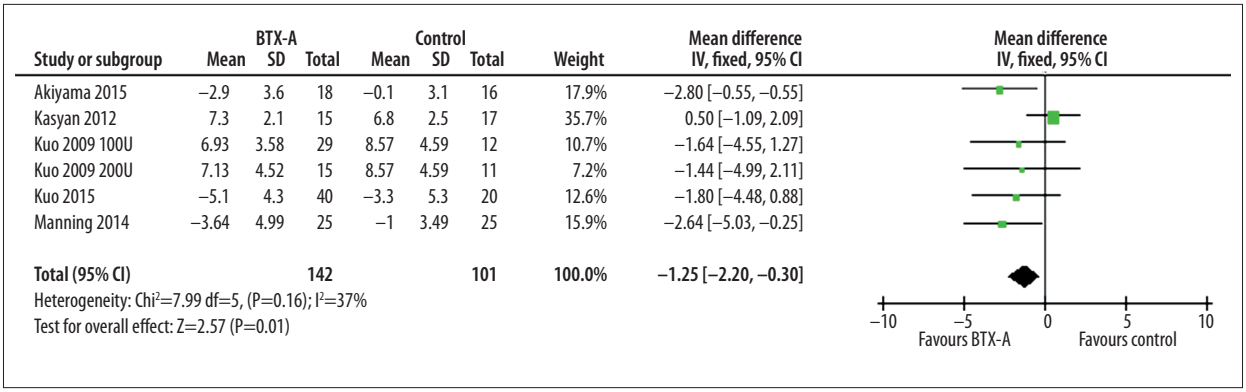

Figure 3. Forest plot of the Interstitial Cystitis Problem Index.

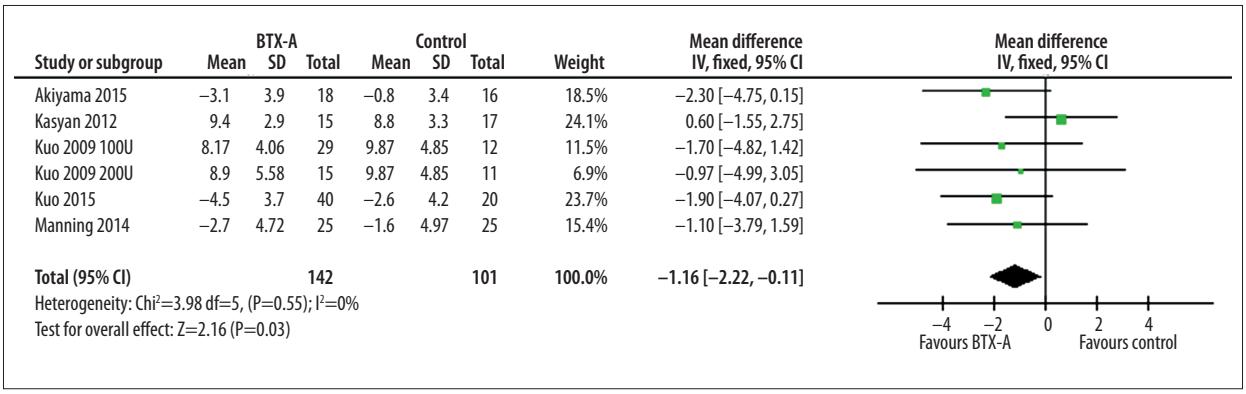

Figure 4. Forest plot of the Interstitial Cystitis Symptom Index.

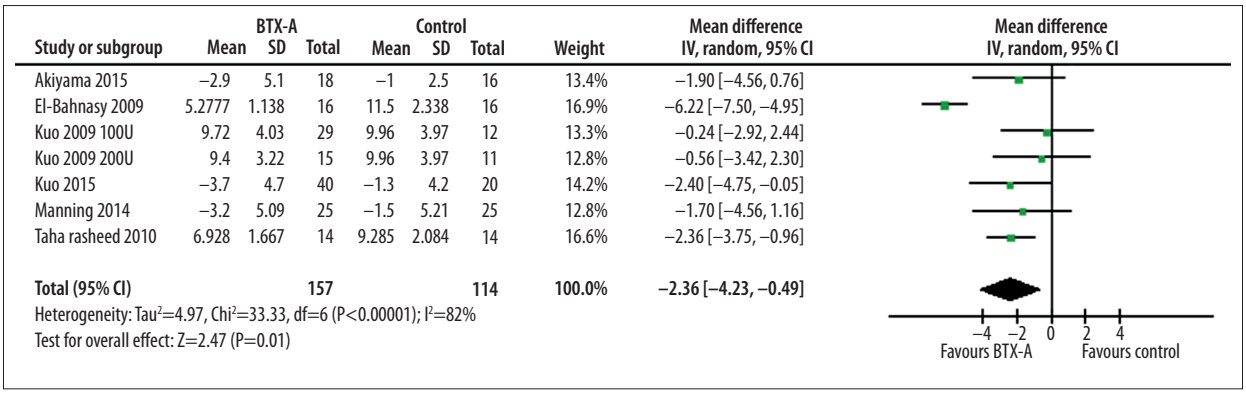

Figure 5. Forest plot of daytime frequency.

Figure 5), but no significant difference in nocturia (WMD –0.79; 95% CI –1.74 to 0.16; p=0.10; Table 2; Supplementary Figure 3).

Maximum cystometric capacity and maximal urinary flow rate

Five RCTs reported baseline and post-treatment MCC [10,13,14,16,19]. Pooled analysis showed significant improvement in MCC in the BTX-A group (WMD 50.49 mL; 95% CI 25.27 to 75.71; p <0.00001; Figure 6). Pooling data across the 3 RCTs that reported the Qmax detected no significant difference between the 2 groups (WMD –1.65 mL/s; 95% CI –6.22 to 2.92; p=0.48) (Supplementary Figure 4) [11,14,16].

Adverse events

Post-void residual urine

Four RCTs evaluated the post-treatment PVR [11,14,16,19]. Pooled analysis showed a significantly larger PVR in the BTX-A group compared with the control group (WMD 10.94 mL; 95% CI 3.32 to 18.56; p=0.005; Figure 7).

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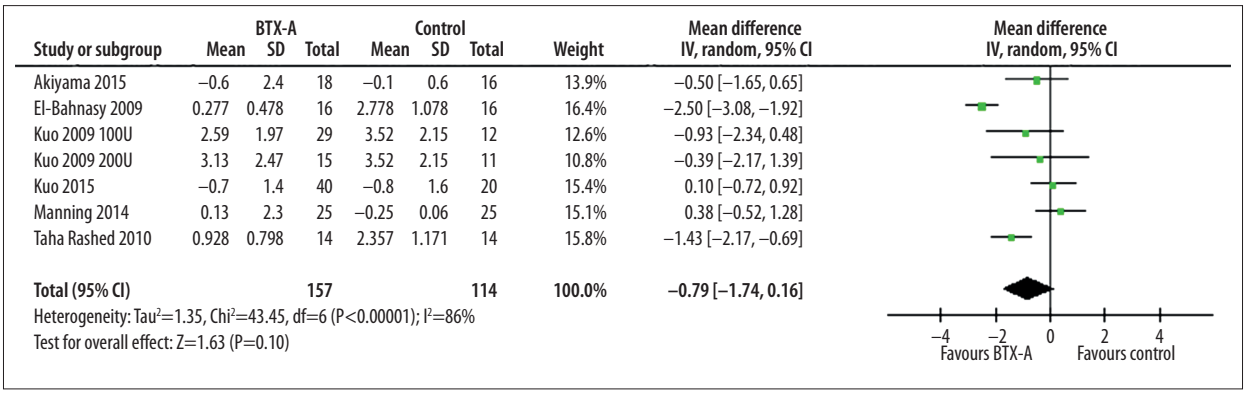
Table 2. Results of meta-analysis comparison of BTX-A and control.

Outcomes of interest	Studies, no.	BTX-A patients, no.	Control patients, no.	WMD/RR (95% CI)	p value*	Study heterogeneity			
						χ^2	df	I^2, %	p value*
Primary outcomes									
VAS score	6	183	134	–1.73 (–3.16 to –0.29)	**0.02**	35.7	5	86	**<0.00001**
ICPI	6	142	101	–1.25 (–2.20 to –0.30)	**0.01**	7.99	5	37	0.16
ICSI	6	142	101	–1.16 (–2.22 to –0.11)	**0.03**	3.98	5	0	0.55
Secondary outcomes									
Daytime frequency	7	157	114	–2.36 (–4.23 to –0.49)	**0.01**	33.33	6	82	**<0.00001**
Nocturia	7	157	114	–0.79 (–1.74 to 0.16)	0.1	43.45	6	86	**<0.00001**
MCC, ml	6	141	98	50.49 (25.27 to 75.71)	**<0.00001**	9.08	5	45	0.11
Qmax, ml/s	4	99	60	–1.65 (–6.22 to 2.92)	0.48	11	3	74	**0.01**
Adverse events									
PVR, ml	5	117	76	10.94 (3.32 to 18.56)	**0.005**	5.57	4	28	0.23
Dysuria	4	132	84	4.88 (0.82 to 28.86)	0.08	9.5	3	68	**0.02**
UTI	5	128	111	1.95 (0.76 to 4.99)	0.17	2.88	4	0	0.41

BTX-A – botulinum toxin A; VAS – visual analog scale; ICPI – Interstitial Cystitis Problem Index; ICSI – Interstitial Cystitis Symptom Index; MCC – maximum cystometric capacity; Qmax – maximal urinary flow rate; PVR – post-void residual urine; UTI – urinary tract infection; WMD/RR – weighted mean difference/relative risk. * Statistically significant results are shown in bold.



Supplementary Figure 3. Forest plot of nocturia.

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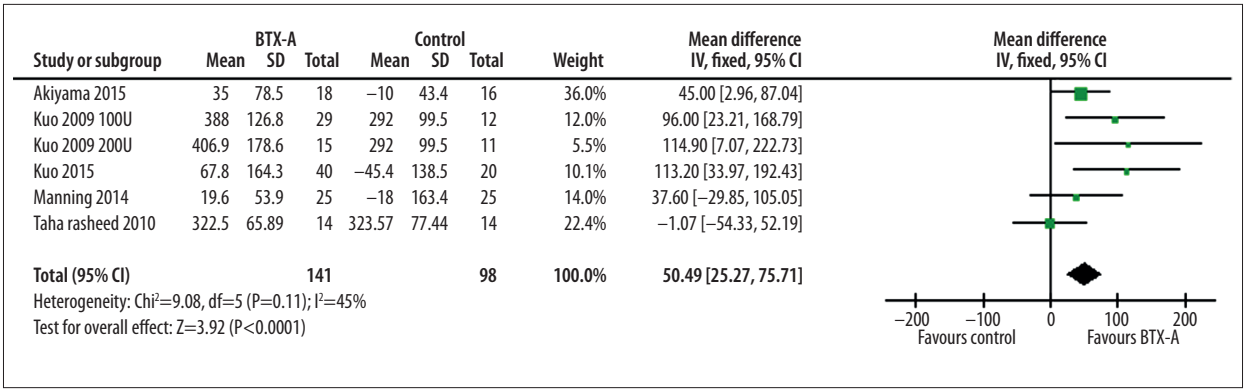
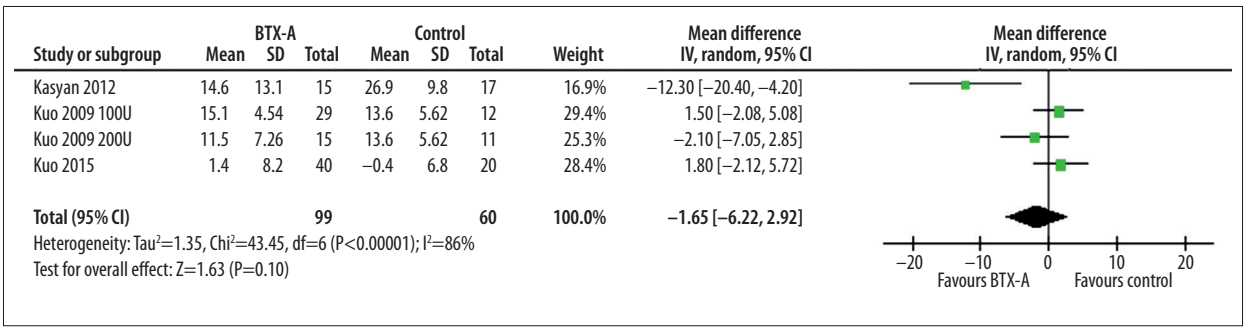


Figure 6. Forest plot of maximum cystometric capacity.



Supplementary Figure 4. Forest plot of maximal urinary flow rate.

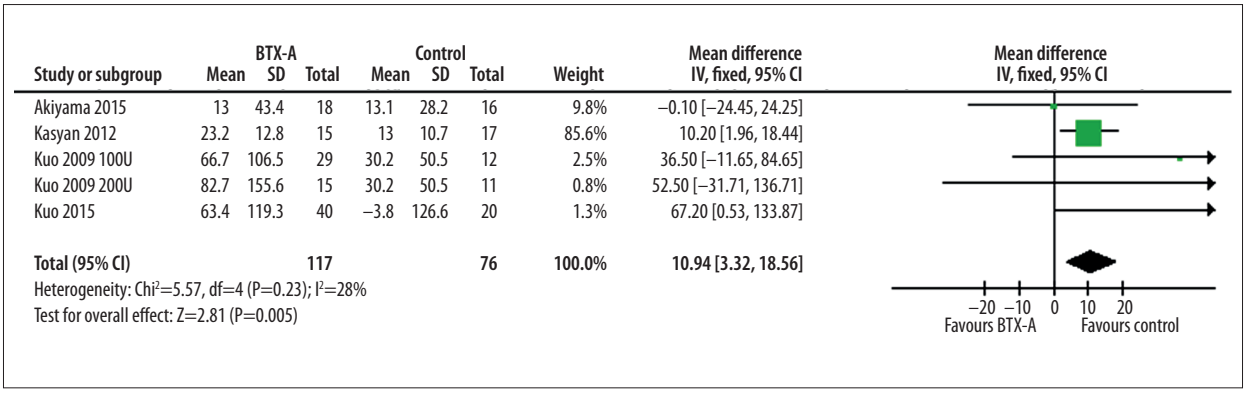


Figure 7. Forest plot of post-void residual urine.

Dysuria

Dysuria data were available in 3 RCTs [14–16]. Pooled analysis identified no significant difference between the 2 groups (RR 4.88; 95% CI 0.82 to 28.86; p=0.08) (Supplementary Figure 5).

Urinary tract infection

Four RCTs reported the UTI rate in the BTX-A and control group [10,14–16]. The pooled RR was 1.95 (95% CI 0.76 to 4.99; p=0.17) (Supplementary Figure 6), indicating no significant difference in the risk of UTI between the 2 groups.

Discussion

This meta-analysis of 7 RCTs and 1 retrospective study assessing the efficacy of BTX-A for BPS/IC showed that BTX-A was associated with a significant improvement in pelvic pain, ICPI, ICSI scores, MCC, and daytime voiding frequency, and with a slightly larger PVR. There was no significant difference in nocturia, Qmax, dysuria, or rate of UTI between BTX-A and controls.

Pelvic pain seriously affects BPS/IC patients' quality of life and could drive other symptoms, such as daytime frequency and nocturia [1,20]. Our meta-analysis suggests that intravesical

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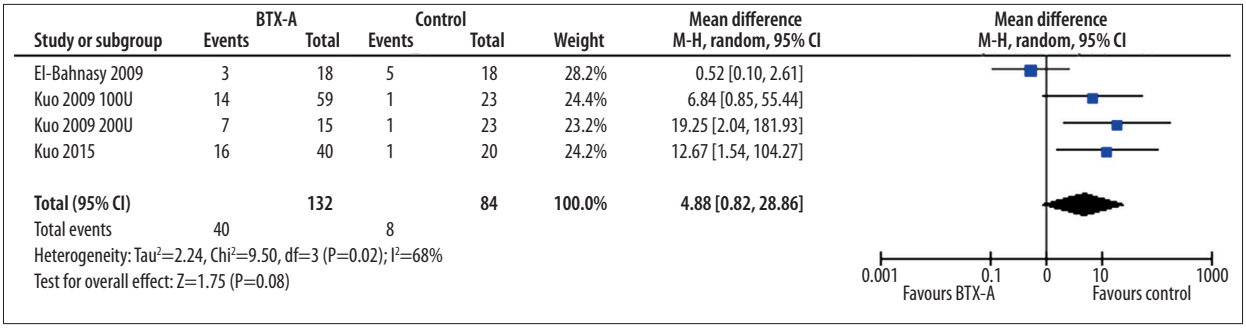
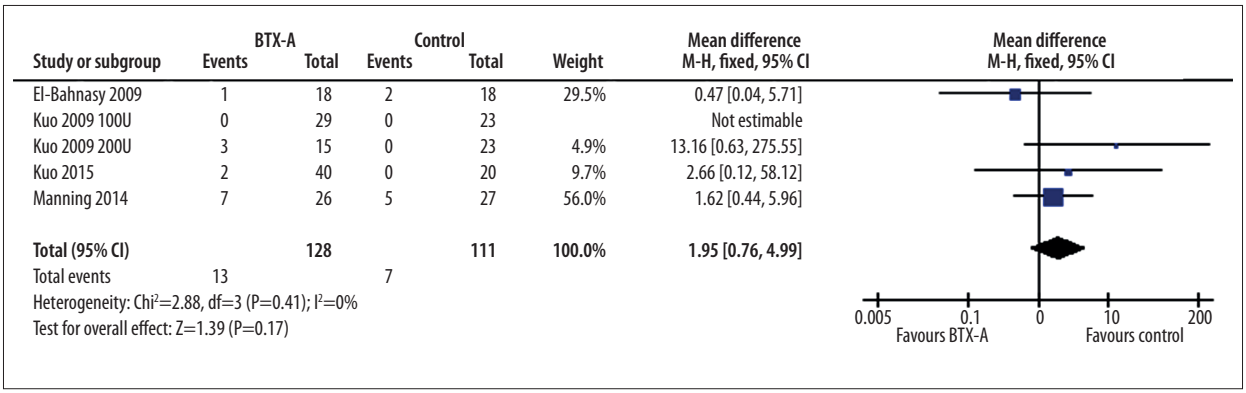


Supplementary Figure 5. Forest plot of dysuria occurrence.



Supplementary Figure 6. Forest plot of urinary tract infection occurrence.

BTX-A injections effectively alleviate pelvic pain. The pain-relieving mechanism of BTX-A is complex. Recent studies have shown that BTX-A significantly improves pain by inhibiting the release of several neurotransmitters from sensory afferent terminals, including glutamate, substance P, and calcitonin gene-related peptides [8,21]. Additionally, there is a decrease in urothelial adenosine triphosphate after BTX-A administration; adenosine triphosphate is released from the bladder urothelium and causes pain by binding to receptor P2X3 in suburothelial sensory neurons [22,23]. Nerve growth factor and brain-derived neurotrophic factor are neurotrophic agents with nociceptive activity that are increased in the urine of patients with BPS/IC [5,24,25]; intravesical BTX-A injections reduced urinary levels of nerve growth factor and brain-derived neurotrophic factor, providing another potential explanation for the analgesic property of BTX-A [5]. In a rat model of chronic bladder inflammation, BTX-A administration reduced C-fos expression, suggesting that BTX-A diminished the activity of nociceptive nerves [26].

The ICPI and ICSI have been widely recognized as reliable, valid, and responsive instruments to assess IC/PBS symptoms [27]. The significant improvements in ICSI and ICPI scores after BTX-A injections show the remarkable influence of BTX-A on subjective symptoms.

The pooled analysis demonstrated that BTX-A injections were associated with a significant reduction in daytime voiding frequency. This is encouraging, as urinary frequency in daily life can severely lower the rate of productivity, prevent participation in social activities, and generate considerable anxiety of social disgrace. This improvement of daytime voiding frequency may be caused by a reduction in the sensation of the bladder and the increase in MCC after BTX-A injections [5,14,28–30].

Pooled analysis of urodynamic variables demonstrated that BTX-A was associated with a significantly increased MCC. By cleaving synaptosome-associated protein 25 kDa, BTX-A inhibits exocytosis of acetylcholine from the vesicles at neuromuscular junctions [31]. When injected into the bladder wall, BTX-A prevents the release of acetylcholine in the detrusor muscle, thus reducing muscle contractions [8,32]. In addition, BTX-A may decrease the bladder sensibility through inhibiting sensory nerve neurotransmitters release [8]. The mechanisms mentioned above may account for the improvement in MCC after BTX-A administration.

A potential disadvantage of BTX-A administration is an increased PVR. The increased PVR may be associated with the impairment of detrusor contractility induced by BTX-A. This undesirable complication is reported to be related to drug dosage [33], and should be avoided by decreasing the dose or by dilation.

The other concern with intravesical BTX-A injections is that this procedure might induce UTI and dysuria. However, pooled

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analysis showed no significant differences in rates of UTI and dysuria between those injected with BTX-A and controls, indicating that BTX-A injections are safe for BPS/IC. This result is very important, as UTI is thought to worsen symptoms of BPS/IC [34]. In 2 included RCTs, patients were prescribed prophylactic antibiotics in the perioperative period [10,14]; this method is effective in preventing UTI, and should be suggested for use accompanying BTX-A injections.

Our meta-analysis may be hampered by the following limitations. First, there was a relatively limited number of controlled trials, the sample sizes of included trials were quite small, and few RCTs reported methods of randomization and blinding. Many of the included RCTs might have used appropriate measures to prevent bias, but failed to report them. Second, it should be recognised that we are unaware of the optimal dose of BTX-A for IC/BPS. The dosage of BTX-A used in the included studies were not identical, which might have influenced the outcomes. Third, BPS/IC is a chronic disease and all of the included trials had relatively short follow-up, so the long-term benefit of BTX-A injections remains to be demonstrated.

To the best of our knowledge, this meta-analysis is the first to assess the efficacy of intravesical BTX-A injections for patients with BPS/IC. The main strengths of the present meta-analysis are multiple and rigorous search strategies, and strictly evaluating the methodological quality of all available controlled studies.

Conclusions

This meta-analysis indicates that intravesical BTX-A injections may be an effective and safe treatment for patients with BPS/IC. BTX-A injections may be associated with significant improvement in pelvic pain, ICPI, ICSI scores, daytime frequency, and MCC, without significant dysuria and UTI occurrence. The slight increase in PVR after BTX-A injections should be carefully monitored. Nevertheless, due to the inherent limitations of the included studies, our findings of the efficacy of BTX-A should be interpreted with caution. Further well-designed, large-scale RCTs with long-term follow-up are required to confirm the findings of this meta-analysis.

Conflict of interests

None declared.

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