Int Urogynecol J (2017) 28:515–525
DOI 10.1007/s00192-016-3079-4

REVIEW ARTICLE

Intravesical treatment for interstitial cystitis/painful bladder syndrome: a network meta-analysis

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Received: 6 March 2016 / Accepted: 14 June 2016 / Published online: 10 September 2016

Abstract
Introduction and hypothesis Interstitial cystitis/painful bladder syndrome (IC/PBS) is a chronic inflammatory condition of the submucosal and muscular layers of the bladder. So far, there is no effective and targeted treatment strategy for IC/PBS. This study aimed to assess the efficacy and safety of intravesical instillation treatment in IC/PBS patients.
Methods We searched various databases up to October 2015. A network meta-analysis was performed to compare global response assessment (GRA) for different treatment strategies, including botulinum toxin A (BoNTA), bacillus Calmette–Guerin (BCG), resiniferatoxin (RTX), lidocaine, chondroitin sulfate (CS), oxybutynin, and pentosan polysulfate (PPS). A traditional meta-analysis was also performed.
Results Sixteen trials evaluating 905 patients were included. Network meta-analysis indicated that BoNTA had the highest probability of being the best treatment course according to GRA assessment results (probability 81.7 %). BCG or BoNTA therapy yielded significant improvement in GRA incidence according to traditional meta-analysis. Patients who received PPS showed higher urinary frequency results compared with the placebo groups. BCG- and PPS-treated patients had elevated urinary urgency treatment effects compared with placebo groups. Bladder capacity restoration results also showed significant improvements in patients who received BoNTA compared with placebo-treated individuals.
Conclusions These findings indicate that BoNTA therapy has the highest probability of being the best therapy according to GRA, and significantly improves bladder capacity in IC/PBS patients. BCG treatment also significantly increases the incidence of GRA and improves the symptoms of urinary urgency. PPS can significantly improve urinary frequency and urgency symptoms in IC/PBS patients.

Keywords Interstitial cystitis · Painful bladder syndrome · Intravesical treatment · Clinical trials · Meta-analysis

Introduction

Interstitial cystitis/painful bladder syndrome (IC/PBS) is characterized by a constellation of bladder symptoms, including urinary frequency, urgency, increased nocturia, and bladder and pelvic pain [1]. The incidence of IC/PBS is variable, with morbidity rates of 3–4 per 10 million in Japan, 18 per 10 million in Europe, and 60–70 per 10 million in the USA [2]. Epidemiological studies demonstrated that IC/PBS morbidity is related to race, age, and gender, further suggesting that the disease most likely affects 30- to 50-year-old women [1, 2]. Furthermore, diagnostic criteria are variable in different countries [3]. The pathogenesis of IC/PBS remains unclear; possible pathogenic factors include infection, autoimmune disease, mast cell infiltration, neurogenic mechanism, change in mucosal epithelial permeability, and glycosaminoglycan metabolism defect [4, 5].

To date, the main purpose of IC/PBS treatment is to restore bladder function, prevent recurrence, and improve the quality of life. There are numerous treatments for IC/PBS, including diet therapy, behavior adjustment training (BAT), oral medication, intravesical instillation, and surgical intervention [6].

Electronic supplementary material The online version of this article (doi:10.1007/s00192-016-3079-4) contains supplementary material, which is available to authorized users

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Treatment strategies for IC/PBS are given priority based on empirical evidence, as the mechanism of this ailment remains unclear. Intravesical perfusion, considered a relatively better treatment tool, is a technique in which the drug is spread directly on the inner surface of the bladder to increase its local concentration and active time while reducing the rate of side effects. However, randomized controlled trials (RCTs) assessing intravesical treatment are scarce for every single drug researched, and comparison of the efficacy of drugs remains controversial.

Current intravesical IC/PBS treatment strategies include botulinum toxin A (BoNTA), bacillus Calmette–Guerin (BCG), resiniferatoxin (RTX), lidocaine, chondroitin sulfate (CS), oxybutynin, and pentosan polysulfate (PPS) [7–11]. Previous studies demonstrated that these interventions can relieve the clinical symptoms of IC/PBS and restore bladder function; however, comparative efficacy among these drugs remains undetermined. Although several systematic reviews have been previously published, no clear comparisons of treatment effects obtained with intravesical medicines are available [2, 12–15]. The aim of this network meta-analysis was to assess the comparative efficacy and safety of intravesical medicines in IC/PBS patients using both direct and indirect evidence, and to discuss their future use for IC/PBS patients.

Materials and methods

Search strategy and selection criteria

This review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement [16] issued in 2009. Any RCTs evaluating intravesical instillation in IC/PBS patients were eligible for inclusion, and no restrictions were placed on language or publication status (published or in press). The Medline, EmBase, and Cochrane Library electronic databases were searched for articles published through October 2015, with "interstitial cystitis" OR "painful bladder syndrome" OR "Hunner's ulcer" AND "intravesical" AND "clinical trials" as the search terms. We also conducted manual searches of reference lists from all relevant original articles and reviews to identify additional eligible studies.

The literature search was undertaken independently by two authors and any inconsistencies were settled by group discussion until a consensus was reached. A study was included if the following criteria were met:

1. RCT design
2. Assessment of intravesical treatment for IC/PBS patients
3. Outcomes included global response assessment (GRA) and one of the following: pain, urinary frequency, urinary urgency, or bladder capacity restoration

Cohort, case–control, and case series studies, in addition to reviews and editorials, were excluded owing to uncontrolled confounders.

Data collection and quality assessment

Two reviewers independently extracted all data, with disagreements resolved in consultation with third-party investigators. The following items were extracted from the articles included: first author name, publication year, country, patient number, patient gender, age, disease type, interventions, controls, additional treatment regimens, and duration of the follow-up period. The primary outcome was GRA; secondary outcomes included pain assessment, urinary frequency, urinary urgency, and bladder capacity. Two reviewers independently assessed the quality of the studies included according to the Cochrane risk of bias tool in the following six domains: selection, performance, detection, attrition, reporting, and other bias [17].

Statistical analysis

For traditional meta-analysis, the inverse variance method was used to pool continuous data; the Mantel–Haenszel method was utilized for dichotomous data. Results were presented as standardized mean difference (SMD) with 95 % confidence intervals (CIs) and odds ratio (OR) with 95 % CIs. In the network meta-analysis, a random-effects network meta-analysis was used for mixed multiple treatment comparisons, fully preserving the within-trial randomized treatment comparison of each trial [18].

The I^2 index was calculated to evaluate the extent of variability attributable to statistical heterogeneity between trials. In the absence of statistical heterogeneity ($I^2 <$ 50 %), a fixed-effect model was used in traditional meta-analysis; otherwise, we used a random-effects model [19, 20]. Consistency within every closed triangle or quadratic loop was investigated using a loop-specific approach in the network meta-analysis. During analysis, inconsistency factors and 95 % CIs were used to determine their compatibility with zero [21]. Predictive intervals (PIs) provide an interval in which future observations will fall [22]. 95 % PIs were examined to capture the uncertainty and magnitude of heterogeneity in the network meta-analysis [23]. To rank the treatments for an outcome, surface under the cumulative ranking (SUCRA) probabilities was used [24]. A "comparison-adjusted" funnel plot was used to assess the presence of small-study effects in the network meta-analysis [25]. Two-tailed $p < 0.05$ was considered statistically significant. Review Manager (version 5.3) and STATA (version 12.0) were used for data analysis.

Results

The literature research returned 229 hits after removing duplications; of these, 16 trials were included in the meta-analysis (Fig. 1). After a full-text review, the reasons for excluding reports were non-RCTs [4, 26], other intervention interference [27, 28], other similar diseases [9, 29, 30], and lack of desired outcome assessment [31]. The general characteristics of the studies included are presented in Table 1.

Of the trials included, 4 reported BCG compared with placebo [32–35], 3 evaluated BoNTA in comparison with placebo [8, 36, 37], 2 reported RTX compared with placebo [38, 39], 2 comparatively assessed chondroitin sulfate and placebo [7, 40], 2 reported PPS compared with placebo [5, 41], 1 evaluated lidocaine compared with placebo [42], 1 reported oxybutynin compared with placebo [43], and 1 assessed BCG in comparison with BoNTA [44]. The studies included assessed 905 patients in all. Female patients accounted for at least 77 % of all subjects, who were all 18 years or older, excluding one study that did not mention patient age [35]. One study had a three-arm design, and included 0.05 μM RTX, 0.1 μM RTX, and placebo control groups [38]; another study had a four-arm design, and included 0.01 μM RTX, 0.05 μM RTX, 0.1 μM RTX, and placebo control groups [39]. Five studies identified additional treatments in both groups, including hydrodistention [8, 37], oral PPS [5, 41], and antibiotics [45]. The shortest and longest follow-up times were 29 days and 24 months respectively (Table 1). All the studies included were RCTs. A summary graph of bias risks for each study is shown in Fig. 2.

Eligible comparisons for overall treatment response in the network meta-analysis are presented in Fig. 3, showing predominantly pairwise comparisons of various drug treatments for IC/PBS. This figure weights the nodes according to the number of patients who received each treatment, and the edges according to the mean control group risk for all comparisons versus placebo. The contribution plot for this network meta-analysis is shown in Fig. 4; BCG versus placebo had the highest contribution for the entire network meta-analysis (14.8 %). The inconsistency plot was produced with an assumed loop-specific heterogeneity estimate, and the exp(IF) (RORs of direct and indirect estimates) shows no significant inconsistency in the network meta-analysis (ROR = 1.534; 95 % CI 1.00–16.53; $\zeta^2 = 0.117$; $p = 0.725$; Fig. 5).

The traditional meta-analysis for BCG versus placebo had similar results with network meta-analysis data (traditional [OR = 2.58, 95 % CI 1.50–4.42; $p = 0.001$]; network [OR = 2.50, 95 % CI 1.47–4.25; $p = 0.001$]), BoNTA vs control (traditional [OR = 6.12, 95 % CI 2.11–17.79; $p = 0.001$]; network [OR = 6.49, 95 % CI 2.53–16.63;

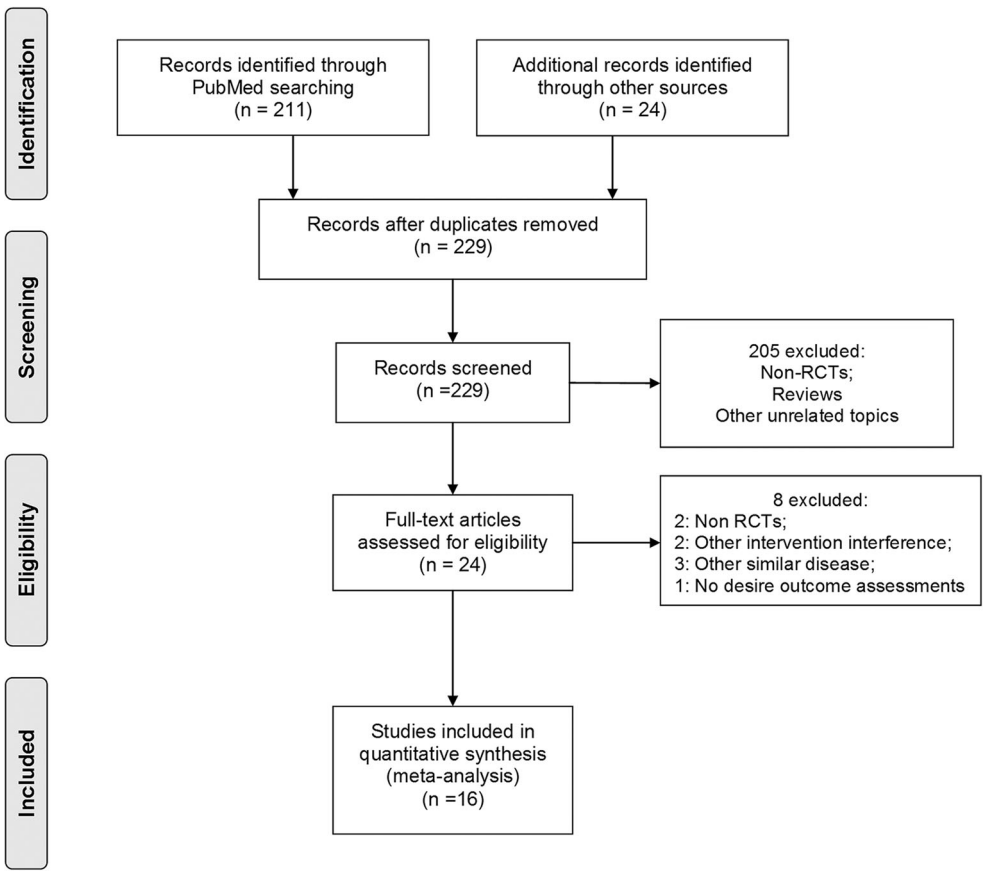

Fig. 1 Flow diagram: preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram

Table 1 Characteristics of the trials included

Reference	Year	Country	No. of patients (experiment number)	Gender of patients (% female)	Age (years)	Type of disease	Experimental group	Control group	Additional therapy	Follow-up
BCG										
Peters et al. [32]	1997	USA	33 (17)	100	23–71	IC/PBS	BCG	Placebo	N/A	6 months
Mayer et al. [33]	2005	USA	265 (131)	81.9	47.7 (13.5)	IC	BCG	Placebo	N/A	31–34 weeks
Irani et al. [34]	2003	Iran	30 (15)	100	38.4 (13.4)	IC	BCG	Placebo	N/A	24 months
Propert et al. [35]	2008	USA	38 (22)	80	N/A	IC	BCG	Placebo	N/A	68 weeks
BoNTA										
Gottsch et al. [36]	2011	USA	20 (10)	100	22–62	IC/PBS	BoNTA	Placebo	N/A	3 months
Manning et al. [37]	2013	Australia	53 (26)	100	53	IC/PBS	BoNTA	Placebo	Hydrodistention	3 months
Kuo et al. [8]	2015	China	60 (40)	86.7	50.8 ± 13.9	IC/PBS	BoNTA	Placebo	Hydrodistention	8 weeks
RTX										
Chen et al. [38]	2005	Canada	22 (10; 8)	77.3	18–85	IC/PBS	RTX 0.1 μM, 0.05 μM	Placebo	N/A	12 weeks
Payne et al. [39]	2005	USA	163 (43; 41; 35)	86	47	IC/PBS	RTX 0.01 μM, 0.05 μM, 0.1 μM	Placebo	N/A	12 weeks
Chondroitin sulfate										
Nickel et al. [40]	2010	Canada	65 (33)	98.50	44.4–45.5	IC/PBS	Chondroitin sulfate	Placebo	N/A	12 weeks
Nickel et al. [7]	2012	Canada	98 (49)	100	45.6 (14.3)	IC/PBS	Chondroitin sulfate	Placebo	N/A	11 weeks
Lidocaine										
Nickel et al. [42]	2008	UK	102 (50)	97	18–75	IC/PBS	Lidocaine	Placebo	N/A	29 days
PPS										
Bade et al. [41]	1995	Netherlands	20 (10)	100	53.8	IC/PBS	PPS	Placebo	N/A	3 months
Davis et al. [5]	2007	USA	41 (21)	100	26–45	IC/PBS	Pentosan polysulfate	Placebo	Oral PPS	18 weeks
Oxybutynin										
Bade et al. [41]	1996	Netherlands	22	95.4	32–80	IC/PBS	Oxybutynin	Placebo	Oral PPS	5.7 months
BCG vs BoNTA										
El-Bahnasy et al. [45]	2009	Egypt	36	100	>18	IC/PBS	BCG	BoNTA	Oral antibiotics	23 weeks

BCG bacillus Calmette–Guerin, *BoNTA* botulinum toxin A, *RTX* resiniferatoxin, *PPS* pentosan polysulfate, *PBS* painful bladder syndrome, *IC* interstitial cystitis, *N/A* not available

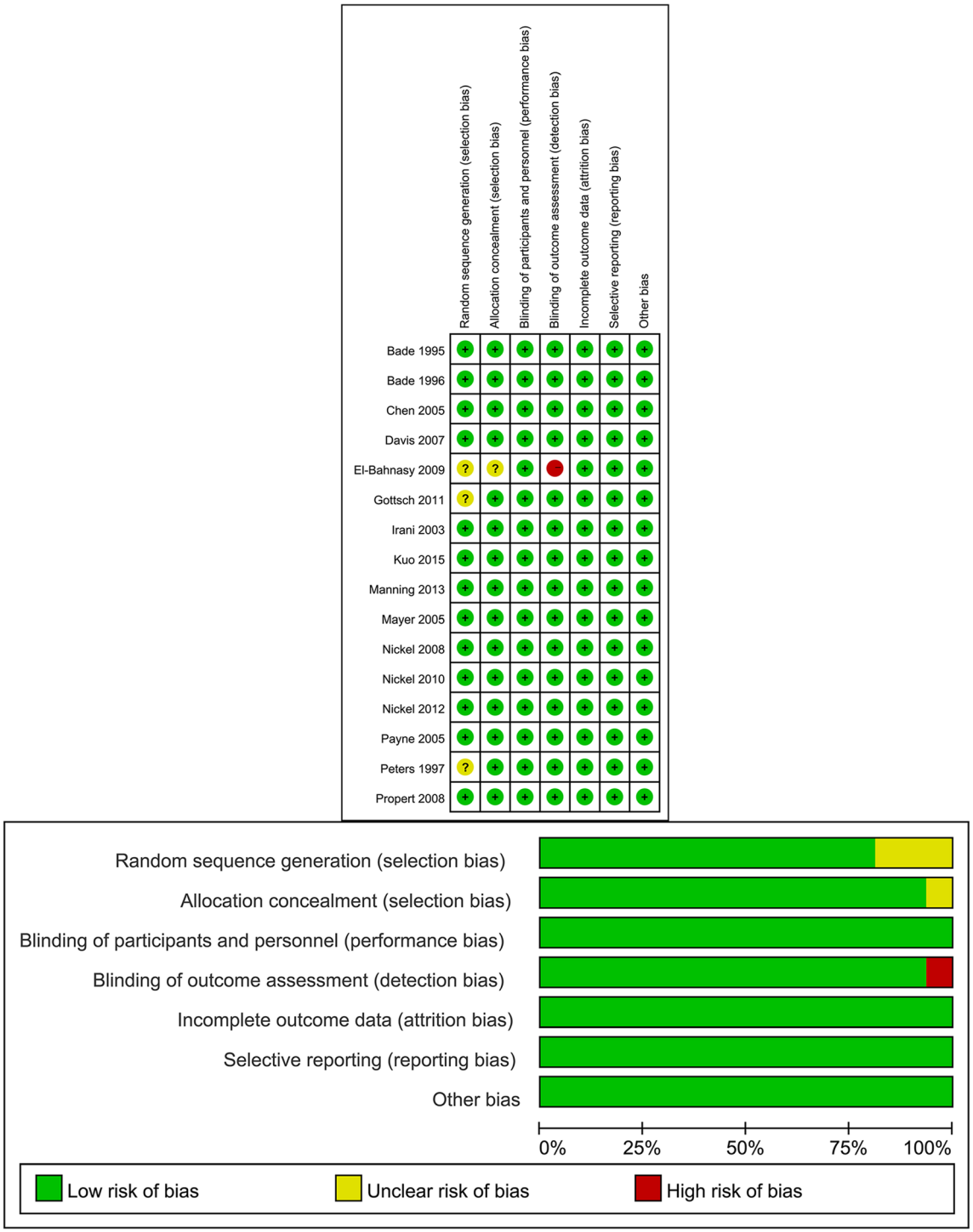

Fig. 2 Methodological quality of trials included in the meta-analysis: risk of bias graph and summary

$p < 0.001$]). In addition, the current network meta-analysis showed significant comparisons between BCG vs RTX (OR = 3.74, 95 % CI 1.53–9.15; $p = 0.004$) and BoNTA vs RTX (OR = 9.69, 95 % CI 2.96–31.71; $p < 0.001$; Fig. 6). We also ranked the comparative effects of all treatments for IC/PBS with SUCRA probabilities (%). Interestingly, BoNTA had the most likely chance of being the best therapy (probability of 81.7 %); the cumulative ranking plots based on our estimates are shown in Fig. 7. The comparison-adjusted funnel plot for assessing publication bias of small-study effects within a network of interventions is depicted in Fig. 8.

In the traditional meta-analysis, GRA results indicated that BCG had a significantly better treatment effect than placebo

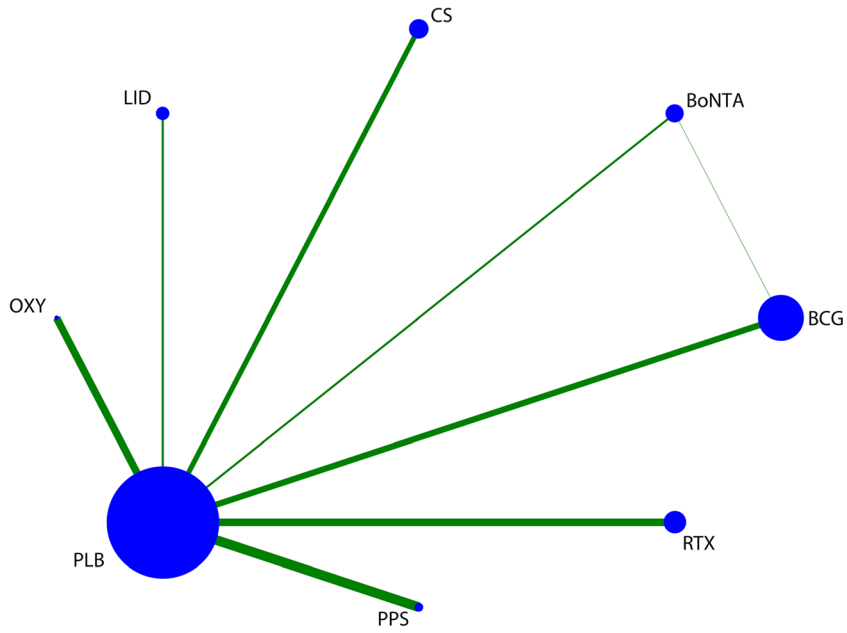

Fig. 3 Evidence network for medicines in the meta-analysis: networks of eligible comparisons for overall treatment response showed predominantly pairwise comparisons of different drug treatments in interstitial cystitis/painful bladder syndrome (IC/PBS). The figure weights the nodes according to the number of patients who have received each treatment and the edges according to the mean control group risk for all comparisons versus placebo. *PLB* placebo, *OXY* oxybutynin, *LID* lidocaine, *CS* chondroitin sulfate, *BoNTA* botulinum toxin A, *BCG* bacillus Calmette–Guerin, *RTX* resiniferatoxin, *PPS* pentosan polysulfate

control (OR = 2.58, 95 % CI 1.50–4.42; $p = 0.001$); BoNTA treatment also had significantly superior effect to placebo control (*OR* = 6.12, 95 % CI 2.11-17.79; $p = 0.001$), while other results showed no significant differences (Figure S1). Pain data revealed that BoNTA had a significant decrease in pain compared with BCG (SMD = 1.39, 95 % CI 0.61–2.61;

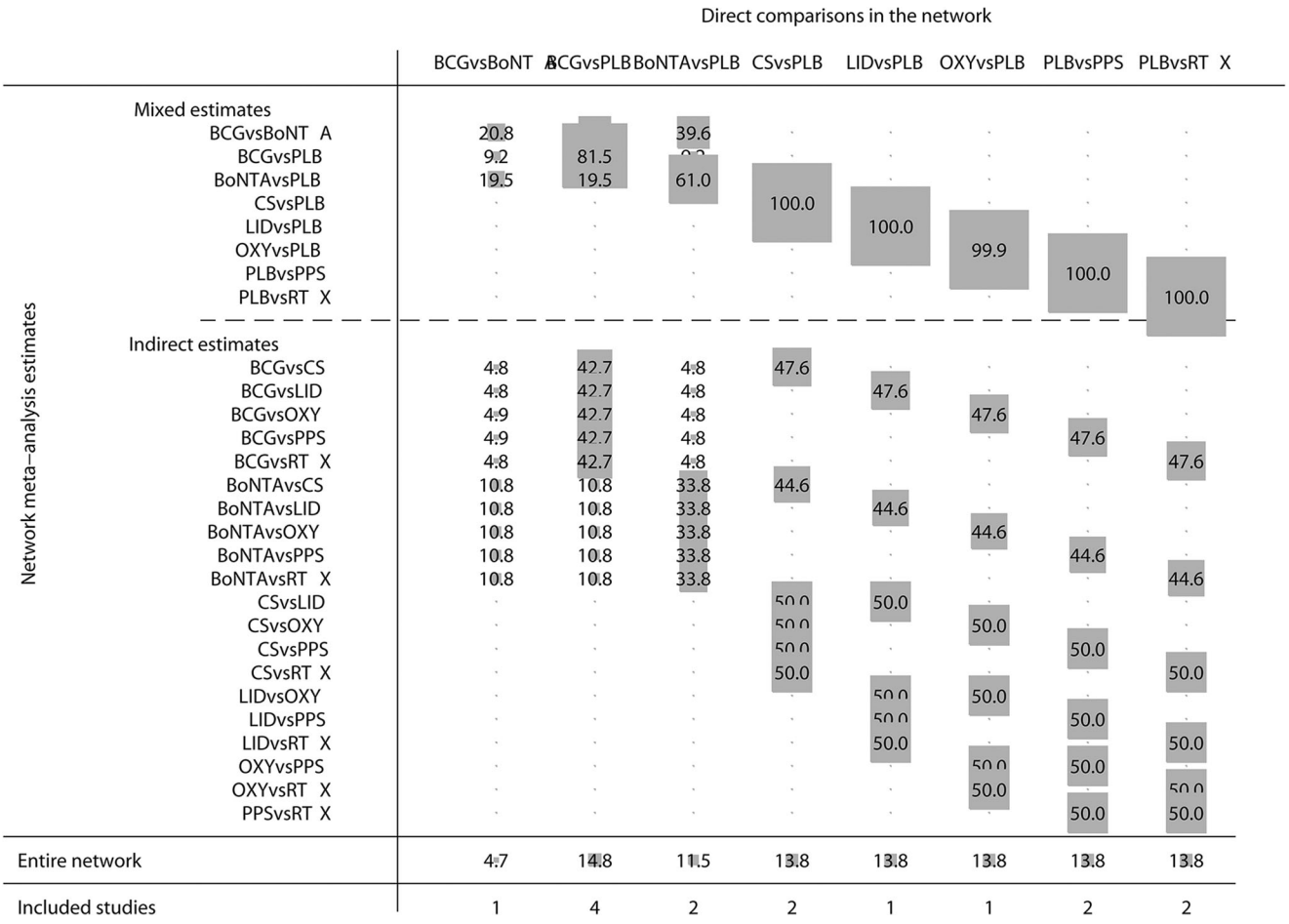

Fig. 4 Forest plot from network meta-analysis showing a summary of the treatment effects in IC/PBS

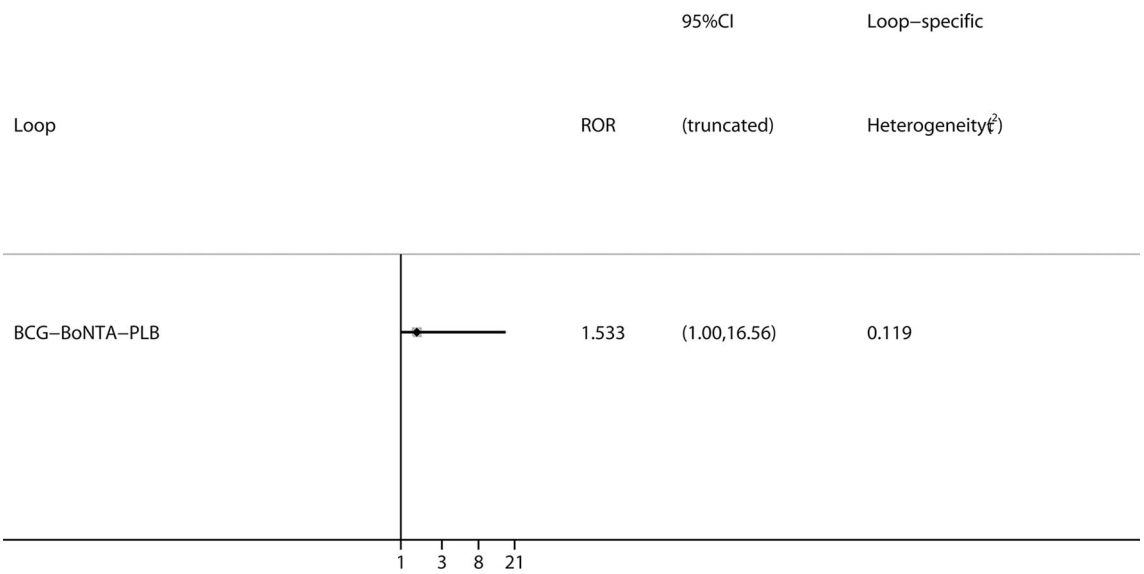

Fig. 5 Cumulative ranking plots based on the estimations from surface under the cumulative ranking (SUCRA) probabilities

$p < 0.001$). However, these results are of very low reliability as they were reported by only one study (Figure S2).

Urinary frequency data showed that the treatment effect of PPS was significantly lower than that of placebo control (SMD = 1.91, 95 % CI 1.17–2.66; $p < 0.001$); BoNTA treatment was significantly superior to BCG intervention (SMD = 3.49; 95 % CI 2.37-4.62; $p < 0.001$), whereas no other significant comparisons were possible (Figure S3). Urinary urgency data showed that BCG treatment was significantly superior to that of placebo control (SMD = −0.59, 95 % CI −1.09–0.08; $p = 0.024$); PPS treatment was also superior to placebo control (SMD = −0.78, 95 % CI −1.42–0.14; $p = 0.016$). Additionally, BoNTA had a better treatment effect compared with BCG intervention (SMD = 2.40, 95 % CI

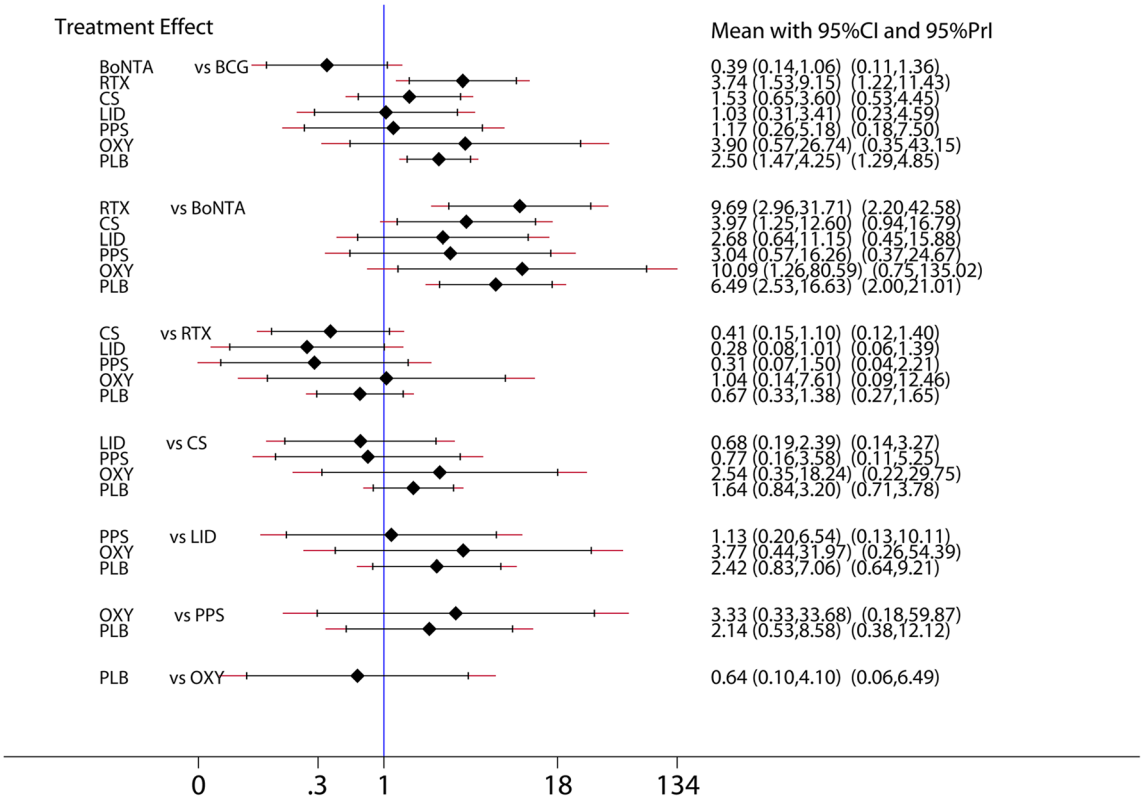

Fig. 6 Contribution plot for this network meta-analysis. Contributions matrix: percentage contribution of each direct or indirect estimate to the network meta-analysis

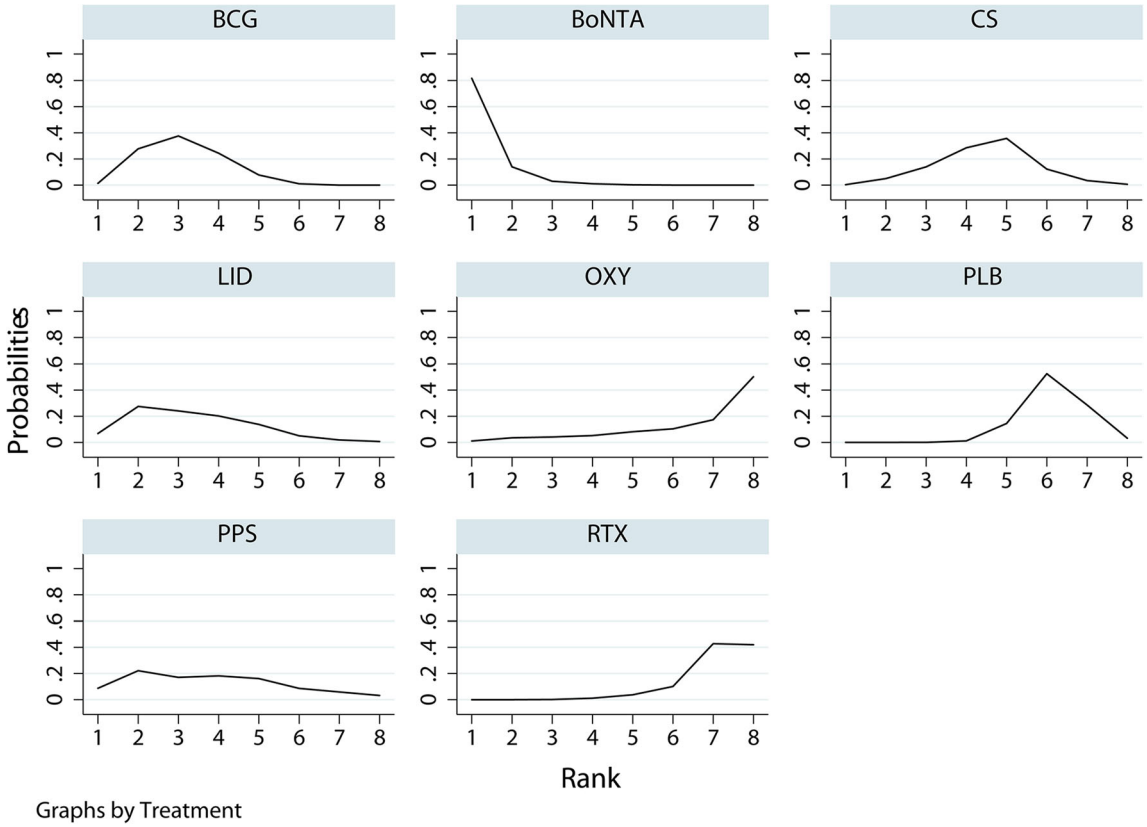

Fig. 7 Inconsistency plot to assume loop-specific heterogeneity

1.48–3.32; $p < 0.001$; Figure S4). Bladder capacity restoration results showed that the BoNTA group showed significant improvement compared with placebo-treated control patients (SMD = 0.53, 95 % CI 0.14–0.92; $p = 0.007$; Figure S5).

Discussion

This updated network meta-analysis included 16 RCTs evaluating intravesical interventions in adult patients with IC/PBS. The findings of the current meta-analysis suggested that:

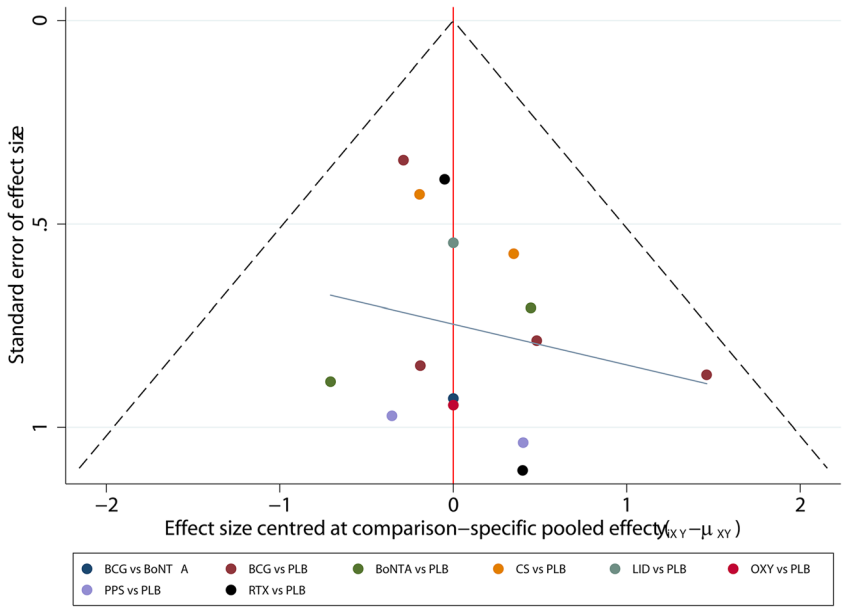

Fig. 8 Comparison-adjusted funnel plot for assessing small-study effects within a network of interventions

1. BoNTA has the highest probability of being the best therapy for improving GRA assessment and significantly ameliorates bladder capacity in IC/PBS patients
2. BCG treatment significantly improves GRA results and symptoms of urinary urgency
3. PPS significantly improves urinary frequency and urgency symptoms in IC/PBS patients

In this research, network meta-analysis was used to assess the therapeutic effects of different medicines in IC/PBS patients for the first time.

In a previous meta-analysis, Dawson and Jamison considered BCG and oxybutynin to be well-tolerated and promising for the intravesical treatment of IC/PBS, whereas RTX, dimethyl sulfoxide (DMSO), and PPS showed no evident effects for most outcomes [2]. Tirumuru et al. suggested that BoNTA might show a trend toward short-term benefit on urodynamic parameters based on RCTs [6]. Giannantoni et al. proposed a comprehensive IC/PBS treatment strategy, such as oral medication, intravesical instillations, and combined treatment, but the results obtained had high heterogeneity, with uncertain conclusions [14]. Matsuoka et al. suggested that BCG therapy could improve most symptoms, but not 24-h urinary frequency [12]. Moreover, Guo et al. considered that RTX could significantly reduce bladder pain, but not improve urinary frequency [13]. According to Dawson and Jamison, DMSO instillations show a non-increase in cystometric capacity, with limited evidence [2]. A recent systematic review based on RCTs still did not clearly indicate the best approach for IC/PBS treatment [43]. Overall, the greatest obstacle in improving IC/PBS treatment stems from the various interventions and diverse outcome assessments, which make results inconsistent. Therefore, an update of these systematic reviews is needed to define the comparison among intravesical treatments.

In this study, the intervention method of the RCTs included was restricted to intravesical instillation treatment because it is widely used as the first line of treatment in IC/PBS patients [44]. We excluded non-RCTs with a high design bias, to increase the reliability of our research, because the treatment and outcome records of IC/PBS are subject to high subjectivity, especially pain and urgency records. We also updated the trials included to incorporate the most recently published review [8], and comparatively analyzed various intravesical treatments by network meta-analysis. However, Peeker et al.'s RCT comparing DMSO and BCG was finally excluded from both network and traditional meta-analyses in this study. Indeed, inclusion criteria in the network meta-analysis mainly focused on overall response, whereas outcome data in the above study were unavailable. Meanwhile, in the traditional meta-analysis, only one high-quality RCT was available, and it could not be taken into account. Moreover, DMSO through intravesical instillation was approved by the United States Food and Drug Administration (FDA) for use in the treatment of IC [46], indicating that there is less controversy over this compound.

This review did not assess oral medications for IC/PBS treatment, mainly because oral medicines include analgesics, hormones, and antidepressants. These drugs can alleviate symptoms; for example, oral PPS showed a relatively positive response in treating pain and urgency symptoms [14]. However, oral medications have limited efficiency, and are usually associated with high rates of side effects, especially oral antidepressants and hormones [13]. Surgery is another option in the treatment of IC/PBS, but is generally utilized when more conservative treatments are not effective. The empirical medicines used in intravesical treatment include local anesthetics (e.g., lidocaine), bladder glycosaminoglycan (GAG) layer repair agent (e.g., heparin, sodium hyaluronate, and CS), anti-inflammatory agents and free radical scavengers (e.g., DMSO), substance P agonists (e.g., RTX), and acetylcholine release inhibitors (e.g., BoNTA). Despite the variety of medicines for IC/PBS treatment, no widely accepted effective treatment is available. In the current network meta-analysis, BoNTA was relatively the best intravesical medicine for IC/PBS with regard to overall treatment response. PPS ranked second highest in the probability of being the best therapy (8.7 %) in this network meta-analysis and lidocaine had the third highest possibility (6.8 %).

In the above traditional meta-analysis, BoNTA, which is extracted from botulinum toxin, significantly improved the GRA of IC/PBS patients compared with placebo. Because of its high molecular weight, BoNTA is limited in the ability to cross the urothelium and reach the suburothelial nervous plexus and bladder smooth muscles; therefore, intravesical instillation has not been applied for routine delivery of BoNTA [47]. According to Gao and Liao [48], combination therapy with intravesical BoNTA injection and hydrodistention plus Cystistat instillation is effective for treating IC/PBS. Additionally, significant improvements in VAS, interstitial cystitis symptom indexes, and frequency were previously reported [49]. Therefore, the intravesical injection of BoNTA is the most effective known treatment for IC/PBS. Bladder capacity was also significantly improved after BoNTA treatment. However, BoNTA showed no treatment advantages with regard to pain, urinary frequency, and urgency results. In one trial, BoNTA showed a significant treatment effect on pain, urinary frequency, and urgency compared with BCG, but these findings require further research for confirmation [45]. The mechanism of BCG in IC/PBS treatment remains unclear though it may be related to local immune system impairment [28]. As shown above, BCG significantly improved GRA and urinary urgency in IC/PBS patients. Other intravesical instillation medicines showed no improvements in GRA. PPS, a heparin-like sulfated polysaccharide, was also approved by the FDA as an oral medicine in IC/PBS treatment [22].

However, PPS by intravesical instillation only showed a therapeutic effect on urinary urgency in this study.

The limitations of this study should be mentioned. First, we had no specific data regarding individuals for any of the trials included; thus, statistical analysis could only be performed for each study. Second, the number of RCTs using a single medicine was limited, which may reduce the reliability of the meta-analysis. Third, heterogeneity in pain outcome was found among the studies included, which may be attributed to the non-standardization of pain assessment. Finally, we were not able to use subgroup analysis and meta-regression to reduce the observed heterogeneity because of the limited number of RCTs assessing single medicines. Therefore, unifying outcome standards is very important in further research.

In conclusion, BoNTA has the highest probability of being the best therapy for IC/PBS according GRA assessment results, and can significantly improve bladder capacity recovery. BCG treatment can also significantly improve GRA incidence and urinary urgency, and PPS can significantly improve urinary frequency and urgency symptoms in IC/PBS patients. Further research would benefit not only from more well-designed RCTs, but also from studies focusing on the pathogenesis and therapeutic mechanisms of IC/PBS to further improve understanding of the disease and its treatments.

Funding None.

Conflicts of interest The authors declare that they have no conflicts of interest.

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