國立臺灣大學公共衛生學院流行病學與預防醫學研究所

碩士論文

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膀胱內藥物治療間質性膀胱炎—系統性回顧及網絡統合分析

Intravesical Therapy for Interstitial Cystitis – A Systematic Review and Network Meta-analysis

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摘要

研究背景與目的：

間質性膀胱炎/膀胱疼痛症候群是一類與膀胱不適疼痛、頻尿急尿等下泌尿道症狀相關的臨床症狀組合統稱。目前病因仍不明，醫界對於什麼是最好的治療方式也尚未達成共識。膀胱內灌注藥物是一種可以緩解臨床症狀並且增加膀胱容量的治療方式，目前用於膀胱內治療的藥物有很多種，本篇系統性回顧將聚焦於比較各種膀胱內的藥物治療，希望收集完整的文獻證據，以網絡統合分析的方式來提供臨床上治療間質性膀胱炎/膀胱疼痛症候群的建議及指引。

研究方法：

本研究採用系統性文獻回顧，在 PubMed、Embase 及 Cochrane Library 等資料庫搜尋比較各種膀胱內灌注藥物用於治療間質性膀胱炎/膀胱疼痛症候群的隨機分派研究。我們使用隨機效應模型的網絡統合分析去比較各種膀胱內灌注藥物包含卡介苗、肉毒桿菌、硫酸軟骨素、肝素、玻尿酸、二甲基亞碸、利多卡因及辣椒素個別使用或合併使用的臨床效果。統計的一致性是使用 sidesplitting 方式。另外，我們使用 SUCRA 方式分析及排序各種藥物的療效；漏斗圖被用來分析有無出版性偏誤。

研究結果：

本研究收錄了 20 個隨機分派研究共 1395 個病人，其中包含了九種膀胱內灌注藥物和安慰劑對照組的比較。網絡統合分析的結果顯示在病人主觀的治療反應這項結果中，「肝素+利多卡因」有最高的可能是最好的治療選擇(可能性 91.8%)；而在降低病人疼痛這項結果中，玻尿酸最可能是最佳的治療(可能性 90.2%)。比較「肝素+利多卡因」及玻尿酸之間的治療效果並沒有顯著差異，而這兩種治療方式能顯著改善病人主觀的治療反應、降低疼痛指數(玻尿酸平均降低 3.6 分；「肝素+利多卡因」平均降低 3.2 分)以及增加膀胱容量(「肝素+利多卡因」平均增加 55.5 毫升；玻尿酸平均增加 57.5 毫升)。另外，肉毒桿菌可以顯著改善整體病人主觀的治療反應、減少間質性膀胱炎症狀指數、減少間質性膀胱炎問題指數、減少頻尿及急尿感次數，以及降低疼痛指數(平均降低 1.88 分)。

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結論：

「肝素+利多卡因」及玻尿酸這兩種治療方式是目前治療間質性膀胱炎/膀胱疼痛症候群最佳的膀胱內灌注藥物選擇，膀胱灌注這兩種藥物組合，可以顯著改善病人主觀的治療效果、減輕疼痛指數以及增加膀胱容量。另外，肉毒桿菌也是一種有效的治療方式，可以改善病人主觀的治療效果、頻尿、急尿感及減輕病人的疼痛。未來仍需要更多標準化的臨床試驗，才能更好地評估比較各種間質性膀胱炎/膀胱疼痛症候群的治療方式及其療效。

關鍵字：間質性膀胱炎、膀胱疼痛症候群、膀胱內灌注治療、臨床症狀、系統性回顧、網絡統合分析

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Abstract

Purpose：

Interstitial cystitis/bladder pain syndrome (IC/BPS) was an unpleasant sensation related to the urinary bladder, associated with lower urinary tract symptoms. The etiology of IC/BPS remains uncertain and there is no consensus regarding the optimal treatment. Intravesical therapy is one of the treatments that can relieve the clinical symptoms of IC/BPS and restore bladder function. The present systematic review will focus on the intravesical therapy with different agents. The goal of this network meta-analysis is to incorporate all available evidence into a general statistical framework to compare the efficacy of intravesical therapies and wish to give some guidance for future treatment choices.

Material and methods：

A systematic literature search was conducted using electronic databases PubMed, Embase, and the Cochrane Library up to and including April, 2018. We did random effects network meta-analysis (NMA) to compare clinical outcomes for different intravesical medications, including Bacillus Calmette-Guerin (BCG), Botulinum neurotoxin A (BoNTA), chondroitin sulfate (CS), heparin, hyaluronic acid (HA), Dimethyl sulfoxide (DMSO), lidocaine, and resiniferatoxin (RTX). The assumption of consistency was assessed by sidesplitting approach. We used the surface under the cumulative ranking (SUCRA) probabilities to rank the outcomes of the treatment. A funnel plot was used to assess the presence of small-study bias in the network meta-analysis.

Results：

Twenty randomized controlled trials with nine intravesical interventions (BCG, BoNTA, CS, DMSO, “HA+CS”, lidocaine, RTX, HA and “heparin + lidocaine”) compared with placebo or non-placebo on a total of 1395 patients, who were mostly female (92%), were included in our analysis. Network meta-analysis indicated that “Heparin + Lidocaine” had the highest probability to be the best therapy (SUCRA probability: 91.8%) and the second place was HA (SUCRA probability: 75.2%) in the assessment of global response assessment (GRA). Besides, HA had the highest probability to be the best therapy (SUCRA probability: 90.2%), followed by “HA+CS”

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(SUCRA probability: 84.5%) and “Heparin + Lidocaine” (SUCRA probability: 82.2%). “Heparin + Lidocaine” and HA both had significant treatment effects than placebo in GRA (“Heparin + Lidocaine”: OR: 55.23, 95%CI: 1.50, 2032.91; HA: OR: 8.3, 95%CI:1.05, 65.53), visual analogue scale for pain (VAS) (“Heparin + Lidocaine”: WMD: -3.2, 95%CI: -4.55 to -1.85; HA: WMD: -3.6, 95%CI: -4.89 to -2.31) and functional bladder capacity (FBC) (“Heparin + Lidocaine”: WMD: 55.5, 95%CI: -43.44 to 67.56; HA: WMD: 57.5, 95%CI: 46.9 to 68.1). However, there was no statistically significant difference between these two treatments according to the network meta-analysis results. Furthermore, BoNTA treatment significantly improved GRA (OR: 4.18, 95%CI: 1.25, 14.17), ICSI (WMD: -1.18, 95%CI: -1.69 to -0.66), ICPI (WMD: -2.58, 95%CI: -3.04 to -2.11), frequency (WMD: -3.34, 95%CI: -6.55, -0.14), urgency (WMD: -2.48, 95% CI: -3.31, -1.66) and VAS (WMD: -1.88, 95% CI: -2.8, -0.96).

Conclusion:

We recommended that “Heparin + Lidocaine” and HA are both the best treatment choices for IC/BPS patients currently, according to the GRA assessment and VAS results. BoNTA is also an effective and reasonable treatment for it significantly improves GRA, ICSI, ICPI, frequency, urgency and VAS. Future researches would be essential to use a standardized design of clinical trials to allow later comparison or combination of data across trials.

Key words: interstitial cystitis, bladder pain syndrome, intravesical therapy, clinical trial, systematic review, network meta-analysis

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Catalog

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List of abbreviations

BCG: Bacillus Calmette-Guerin

BoNTA: Botulinum neurotoxin A

BPS: Bladder pain syndrome

CI: Confidence interval

CS: Chondroitin sulfate

DMSO: Dimethyl sulfoxide

FBC: Functional bladder capacity

GAG: Glycosaminoglycan

GRA: Global response assessment

HA: Hyaluronic acid

IC: Interstitial cystitis

ICSI: Interstitial cystitis symptom index

ICPI: Interstitial cystitis problem index

NMA: Network meta-analysis

OR: Odds ratio

PPS: Pentosan polysulphate sodium

RTX: Resiniferatoxin

RCT: Randomized controlled trial

SUCRA: Surface under the cumulative ranking

WMD: Weighted mean difference

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Introduction

Bladder pain syndrome (BPS), which has been commonly referred to as "interstitial cystitis (IC)", was defined as "An unpleasant sensation (pain, pressure, discomfort) perceived to be related to the urinary bladder, associated with lower urinary tract symptoms of more than six weeks' duration, in the absence of infection or other identifiable causes." [1] Patients with IC/BPS had suffered a lot from the symptoms, which can have a profound, detrimental impact on quality of life[2]. IC/BPS is most commonly diagnosed in the fourth decade or later [3] and it is more common in women than in men with a female-to-male ratio of 10:1[4].

The etiology or pathogenesis of IC/BPS remains uncertain. Various hypotheses have been proposed, such as neurogenic inflammation, mast cell activation, dysfunction of the superficial layer of the extracellular matrix of the glycosaminoglycan (GAG) layer, down-regulation of tight junction proteins, increased urothelial permeability, and psychosomatic factors[5]. To find an effective and specific therapy for IC/BPS is challenging and there is no consensus regarding the optimal treatment [6, 7]. The goal of the management is to provide relief of symptoms in order to achieve a better quality of life. According to the American Urological Association (AUA) 2015 guidelines, a stepwise approach to the management of disease is recommended. The first-line therapeutic approaches include general relaxation, behavior modification, and bladder training; the second-line includes oral medications including Dimethyl sulfoxide (DMSO), Pentosan polysulphate sodium (PPS); the third-line is bladder hydrodistension; the fourth-line intravesical instillation; the fifth-line neuromodulation, and the sixth-line is surgical interventions[2]. The rationale is to move from one level (eg, the first-line to second-line) when less risky approaches have failed. Sometimes, combinations of different treatment methods have been used to improve efficacy.

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The present systematic review will focus on the intravesical therapy, i.e. medication is administered directly into the bladder. The agents used for intravesical therapy were listed below along with its rationale.

(1) Bacillus Calmette-Guerin (BCG): BCG is usually used as an immunotherapy for non-muscle invasive bladder cancer [8]. Immune system dysregulation with an imbalance of Th1 and Th2 cells may also play a role in the pathophysiology of IC/BPS. BCG can stimulate the type 1 helper T-cell cytokine profile and therefore, alleviate the symptoms of IC/BPS [9].

(2) Botulinum neurotoxin A (BoNTA): BoNTA is one of the powerful neurotoxins to inhibit the release of neurotransmitters from the nerve fibers and urothelium [10]. Therefore, BoNTA reduces bladder pain, modulates bladder sensation, and reduces chronic inflammation in the central nervous system, which have been demonstrated in animal and human experiments [11].

(3) Glycosaminoglycan (GAG) substitutions – Chondroitin sulfate (CS), heparin and hyaluronic acid (HA): A defect in the protective bladder's mucus lining of GAG has been documented in a subset of IC/BPS patients [12]. Intravesical instillation of GAGs has produced some symptom relief in patients with IC/BPS with a low risk of systemic adverse effects [13]. Previously, heparin has commonly been used off-label for IC/BPS therapy for relatively low cost. To date, hyaluronan, the salt of hyaluronic acid (HA), and chondroitin sulphate (CS) are the two most commonly used GAGs for intravesical treatment, alone or in combination [13].

(4) Dimethyl sulfoxide (DMSO): DMSO is the only approved drug by the US Food and Drug Administration (FDA) for intravesical use in IC/BPS since 1997. The mechanism of DMSO is thought to be multifactorial, including anti-inflammation, analgesic, collagen dissolution, muscle relaxant, effect on histamine release from mast

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cells [14].

(5) Lidocaine: Lidocaine is an anesthetic agent that has been recognized as having powerful broad-spectrum anti-inflammatory effects, including stabilizing mast cells and blocking histamine release, which is theoretically ideally suited to suppress the neuro-inflammatory cycle occurring in IC/BPS [15].

(6) Resiniferatoxin (RTX): RTX, an ultrapotent capsaicin analogue, acts to desensitize the afferent bladder innervation, which is beneficial to reduce pain, frequency and nocturia in IC/BPS [16].

Previous studies including different regimens (listed above) have shown that these intravesical agents can relieve the clinical symptoms of IC/BPS and restore bladder function [9-11, 14-31]. For reviewing the treatment effects of different intravesical medications, several systematic reviews have been published [5, 32-35]. However, no clear comparisons of treatment effects obtained are available.

The goal of this network meta-analysis is to incorporate all available evidence into a general statistical framework to compare the efficacy of intravesical therapies in IC/PBS patients using both direct and indirect comparisons and wish to give some guidance for future treatment choices.

Material and methods

Literature search

The PICO statement of our study searching is as follows: (1) Population: patients with IC/BPS; (2) Intervention: IC/BPS patients who received intravesical therapy; (3) Comparison: IC/BPS patients who received intravesical normal saline instillation only; (4) Outcome: improvement in global response assessment (GRA), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), pain, urinary

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frequency, urinary urgency, nocturia, or bladder capacity restoration. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Statement (PRISMA) [36] guidelines to perform a comprehensive search for literature on intravesical therapy for IC/BPS. To identify studies for this review, we undertook computer-based literature search within the MEDLINE (via PubMed), EMBASE, and Cochrane Central Register of Controlled Trials (CENTRAL) databases up to and including April, 2018 without any restriction in languages used in publications. The MeSH terms and related synonym including “bladder pain syndrome”, “interstitial cystitis”, “painful bladder syndrome”, “Hunner’s ulcer”, “intravesical therapy”, “intravesical”, “bladder instillation” and “clinical trial” etc., were combined in the search strategy. We also manually searched reference lists of related publications including reviews, meta-analyses, and other articles to include additional eligible studies. Duplicates were removed, and publications that had irrelevant title and abstract, outcomes as well as insufficient information were also discarded. The remaining publications were further accessed by full text articles scanning independently by two authors and any inconsistencies were resolved by discussion until a consensus was reached.

Selection criteria

Inclusion criteria

The trials were considered eligible if they met the following criteria:

(1) Randomized controlled trials (RCTs);

(2) All the patients were diagnosed with IC/BPS according to the Interstitial Cystitis Data Base Study criteria, NIH Urologic Chronic Pelvic Pain Consensus criteria (Baltimore, December 2007), or National Institute of Diabetes and Digestive or

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Kidney Diseases (NIDDK) Criteria for Interstitial Cystitis [37] or American urology association 2015 amendment[2];

(3) Interventions of the studies include only intravesical therapy;

(4) Full texts were available;

(5) Adequate data of necessary information such as treatments and outcomes of patients were provided.

Exclusion criteria

The following criteria were used for data exclusion:

(1) Case reports, letters, comments, meta-analysis, review, and meeting abstracts;

(2) Studies did not include one of the following outcomes: global response assessment (GRA), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), pain, urinary frequency, urinary urgency, nocturia, or bladder capacity restoration;

(3) Trials which combined with other treatment modalities in addition to intravesical agents were excluded.

Statistical analysis

We firstly conducted a standard pairwise random effect meta-analysis for direct evidence. Estimates were presented as odds ratios with 95% confidence intervals (95%CIs) and weighted mean difference (WMD) with 95% confidence intervals (95%CIs). We assessed heterogeneity in these analyses with the I^2 statistics. Then we did random effects network meta-analysis (NMA) by assuming a common heterogeneity for all comparisons. The assumption of consistency was assessed by side-splitting approach. We use the surface under the cumulative ranking (SUCRA)

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probabilities to rank the outcomes of the treatment; SUCRA is the ratio of the area under the cumulative ranking curve to the entire area in the plot. The larger the area of the probability cumulates, the better the treatment effects would be[38]. A funnel plot was used to assess the presence of small-study bias in the network meta-analysis[39]. STATA version 15.0 (Stata Corp LP, College Station, TX) were used for data analysis

Results：

Eligible studies

The entire process of literature search is shown in Fig. 1. A total of 322 studies were obtained from the literature search after removing duplications. 292 studies were excluded due to animal models, reviews or unrelated topics. With the full-text assessment, twenty RCTs with nine intravesical interventions (BCG, BoNTA, CS, DMSO, “HA+CS”, lidocaine, RTX, HA and “heparin + lidocaine”) compared with placebo or non-placebo on a total of 1395 patients, who were mostly female (92%), were included in our analysis. Fifteen trials were two-arm trials, four three-arm trials and one four-arm trial. About the treatment duration, BoNTA and RTX need only once treatment, while other treatments need mostly from 6 weekly to 10 weekly. The timing of follow-up is also diverse from 29 days to 24 months after the last treatment. Main study endpoints included global response assessment (GRA), interstitial cystitis symptom index (ICSI), interstitial cystitis problem index (ICPI), pain, urinary frequency, urinary urgency, nocturia, and bladder capacity restoration. The general characteristics of the included twenty studies were presented in Table 1.

Quality assessment and publication bias

The quality of included studies were assessed in seven domains according to the

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Cochrane Collaboration tool for assessing risk of bias. Four trials with DMSO intervention were used open-label design due to the garlic-like taste of DMSO after intravesical administration, which would have been impossible to mask. The risk-of-bias assessment of the included trials is summarized in Figure 2. We used funnel plot (Fig.3) and Egger's test (Fig 4) to detect small study bias. No evident publication bias was observed on visual or statistical examination.

Network meta-analysis

1. GRA (Global response assessment)

For comparison of the overall treatment response, we use the global response assessment (GRA) as the outcome. The eligible studies were grouped into ten nodes in the network meta-analysis resulting in 13 possible pairs of comparisons (Fig. 5). The ten interventions were: BCG, BoNTA, CS, DMSO, "HA+CS", lidocaine, RTX, HA and "heparin + lidocaine". The size of nodes in the figure is proportional to the number of the patients who received each treatment. And the size of edges represents the number of trials in each comparison. The results from network meta-analysis showed patients in the following groups: BoNTA (OR: 4.18, 95%CI: 1.25, 14.17), CS (OR: 5.13, 95%CI:1.28, 20.48), HA (OR: 8.3, 95%CI: 1.05, 65.53) and "Heparin + Lidocaine" (OR:55.23, 95%CI:1.50, 2032.91) had significantly better treatment response than placebo. Besides, patients treated with "Heparin + Lidocaine" also had superior improvement than patients treated with RTX (OR: 83.76, 95%CI: 1.25, 5596.02). However, there is no known significant results found in other treatment comparisons (Table 2). We ranked the comparative treatment effects with SUCRA probabilities (%). "Heparin + Lidocaine" had the highest probability to be the best therapy (SUCRA probability: 91.8%) and the second place would be HA (SUCRA probability: 75.2%).

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The cumulative ranking plots are shown in Fig. 6.

2. ICSI & ICPI

There were nine literatures described the ICSI and ICPI, recruiting of 764 patients (Fig.7 and Fig. 8). Compared with placebo, only BoNTA showed significant improvement in ICSI (WMD: -1.18, 95% CI: -1.69, -0.66), while other treatments did not show statistically difference (Table 3). As for ICPI, patients received BoNTA or Lidocaine had significant improvement compared with patients in placebo groups (BoNTA: WMD: -2.58, 95%CI: -3.04, -2.11; Lidocaine: WMD: -1.63, 95%CI: -3.03, -0.23). Besides, the BoNTA group significantly decreased ICPI than the BCG group (WMD: -2.01, 95% CI: -2.98, -1.03) and the Lidocaine group was significantly superior than the CS group (WMD: -2.24, 95% CI: -4.04, -0.43) (Table 4).

3. Frequency

A total of 16 studies had described the outcome of urinary frequency (Fig. 9). The overall effect showed that only BoNTA significantly decreased urinary frequency compared with placebo (BoNTA: WMD: -3.34, 95%CI: -6.55, -0.14) (Table 5). There were no significant differences in other treatment comparisons.

4. Urgency

As for the urinary urgency, 7 studies reported this outcome (Fig. 10). BCG and BoNTA were significantly better than placebo in reducing the times of feeling urinary urgency (BCG: WMD: -0.65, 95%CI: -1.08, -0.22; BoNTA: WMD: -2.48, 95% CI: -3.31, -1.66), whereas, CS, Lidocaine and RTX were not. Besides, BoNTA is significantly better than BCG in improving urgency (WMD: -1.83, 95%CI: -2.53, -1.13) as well as superior than CS (WMD: -2.48, 95% CI: -4.46, -0.51) and Lidocaine (WMD:

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-1.66, 95% CI: -2.85, -0.48) (Table 6).

5. Nocturia

Six studies reported the nocturia (Fig. 11). Results from our analysis suggested that BCG, BoNTA and RTX might decrease the times of nocturia compared with placebo. However, no significant results were found in all treatment comparisons. (Table 7)

6. Visual analogue scale (VAS)

A total of 13 studies were analyzed the pain with visual analogue scale (VAS) (Fig. 12). Comparing with placebo, patients in groups of BCG, BoNTA, DMSO, "HA+CS", HA and "Heparin + Lidocaine" had significantly decreased pain scores (BCG: WMD: -0.92, 95%CI: -1.7, -0.14; BoNTA: WMD: -1.88, 95% CI: -2.8, -0.96; DMSO: WMD: -1.92, 95%CI: -3.64, -0.2; "HA+CS": WMD: -3.4, 95% CI: -5.91, -0.88; HA: WMD: -3.6, 95% CI: -5.36, -1.84; "Heparin + Lidocaine" WMD: -3.2, 95% CI: -5.0, -1.39) (Table 8). Furthermore, we ranked the comparative treatment effects with SUCRA probabilities (%). Hyaluronic acid (HA) had the highest probability to be the best therapy (SUCRA probability: 90.2%), followed by "HA+CS" (SUCRA probability: 84.5%) and "Heparin + Lidocaine" (SUCRA probability: 82.2%). The cumulative ranking plots are shown in Figure 13.

7. Functional bladder capacity (FBC)

There were four studies, including five pairwise comparisons describing about the restoration of functional bladder capacity (FBC) (Fig. 14). Treatments with HA and "Heparin + Lidocaine" appeared to be more effective in increasing FBC comparing

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with placebo (HA: WMD: 57.5, 95% CI: 46.9, 68.1; “Heparin + Lidocaine”: WMD: 55.5, 95% CI: 43.44, 67.56) or BCG (HA: WMD: 66.5, 95% CI: 32.07, 100.93; “Heparin + Lidocaine”: WMD: 64.5, 95% CI: 29.59, 99.41). But there is no significant difference between HA and “Heparin + Lidocaine”. Besides, HA is significantly better than BoNTA (WMD: 35.1, 95% CI: 0.64, 69.55) (Table 9).

Heterogeneity assessment

We used sidesplitting model to check the inconsistency and it showed that there is inconsistency in our outcome results — GRA and frequency in the network meta-analysis (Fig. S1).

Discussion：

Our review included twenty RCTs for surveying the effects of intravesical therapy for IC/BPS. The main findings of current network meta-analysis concluded that:

1. HA and “Heparin + Lidocaine” both showed significant treatment effects than placebo in GRA, VAS and FBC. In the results of GRA, “Heparin + Lidocaine” had the highest probability of being the best therapy, followed by HA treatment. In addition, HA ranked the best therapy in the results of VAS and “Heparin + Lidocaine” therapy was the third. However, there was no statistically significant difference between these two treatments according to the network results (Table 2 and Table 8). The most eminent impacts of these two treatments: HA and “Heparin + Lidocaine” are decreasing VAS and increasing FBC. With regard to pain control, HA and “Heparin + Lidocaine” decreased 3.6 and 3.2 scores in VAS respectively, comparing with placebo, while BoNTA only reduced 1.69 scores. In addition, HA and “Heparin + Lidocaine” substantially increased FBC around 55 ml, which is

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nearly 150% improvement than baseline (about 100 ml) [40]. Therefore, we recommend HA and "Heparin + Lidocaine" were currently the best treatment options for IC/BPS patients.

2. Although BoNTA treatment ranked behind the HA or "Heparin + Lidocaine" in the outcomes of GRA and VAS, it is still an effective treatment for IC/BPS. BoNTA is significantly superior to placebo in the outcomes of GRA, ICSI, ICPI, frequency, urgency and VAS. Besides, BoNTA needs to be administered only once, while other intravesical medications need several times of bladder instillation in each treatment cycle. This is extremely relevant to improving patient adherence.

However, there were inconsistency found in our analysis about GRA and frequency. The inconsistency in GRA were checked in sidesplitting model, which revealed that the inconsistency existed between treatment BCG vs DMSO and CS vs DMSO (Fig. S1). We thought that only one trial of each one pair comparison is attributed to the inconsistency. To develop a more solid conclusion and get more evidences, it is necessary to conduct more RCTs in the future. As for the inconsistency noted in the outcome of frequency, data from Nickel et. al[41] showed the effects of CS was worse than placebo, however, the results were not statistically significant ($p = 0.2067$). The authors explained that this underpowered results may be attributed to inadequate sample size in each group.

In the previous network meta-analysis, Zhang et al. thought that BoNTA has the highest probability of being the best therapy for improving GRA and ameliorating bladder capacity in IC/BPS patients[42]. However, they exclude the combined regimen and therefore, the effects of "Heparin + Lidocaine" could not be compared with other treatments. Several meta-analyses for each treatment or pairwise treatment comparisons were done before but showed diverse outcomes. In 2007, Dawson and Jamison were

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the first team to acquire the most comprehensive evidence from intravesical therapy for IC/BPS patients[34]. They found that BCG and oxybutynin were the most promising therapy and reasonably well tolerated; while RTX showed no evidence of benefit but caused pain which significantly reduced treatment compliance [34]. Matsuoka et al. reported that BCG could significantly improve symptoms, but no difference in 24-h urinary frequency[35]. Barua et al. considered that high molecular weight hyaluronic acid (HMW-HA) was significantly superior in cost effectiveness and cost efficacy to all other instillation regimes[13]. Giannantoni et al. had proposed a vast search including oral medication, intravesical instillation and combined therapy. The results seemed that BoNTA injections reported a significant decrease in pain as assessed by VAS and frequency. But they finally concluded the evidences were uncertain owing to high heterogeneity[43].

Our study has some limitations. Firstly, the number of included clinical trials was limited. We include only RCTs to minimize the design bias but this largely limited the literature search. Besides, to optimize the quality of our analysis, we only include studied that have comparable and consistent outcomes, which further restrict the scope of search. The greatest difficulties to perform a network meta-analysis for intravesical therapy for IC/BPS patients were the lack of internationally accepted protocols for conducting the randomized controlled trials, which causing currently diverse treatment durations (eg. Once, weekly, biweekly, monthly, etc.), different follow-up periods (from 29 days to 24 months) and various instruments for evaluating treatment response. Secondly, the individual data from each patient cannot be access, and thus, we could only perform the statistics from each study. Thirdly, inconsistency existed in two outcomes of our study. Although we tried to identify the source of inconsistency, but the results may still be influenced. Fourthly, we did not analyze the adverse effects in

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the included studies due to the high heterogeneity. Not every study reported the safety issue of the treatment. No mortality was reported in the included studies and the adverse events were mainly minor complications including urinary tract infection, dysuria or mild hematuria.

Future researches would be of great importance in developing a unified diagnosis criteria or finding a specific biomarker for IC/BPS patients. Besides, using a standardized set of outcome measurements, duration of treatment and follow-up is beneficial to allow later comparison or combination of data across trials. Furthermore, long-term outcomes including how long the treatment effects could sustain and the duration of relapse symptoms were also the crucial issues to investigate.

In conclusion, “Heparin + Lidocaine” and HA seem to be the best treatment choices for IC/BPS patients, based on results of the GRA assessment and VAS. BoNTA is also an effective and reasonable treatment, as it significantly improves GRA, ICSI, ICPI, urinary frequency, urgency and VAS.

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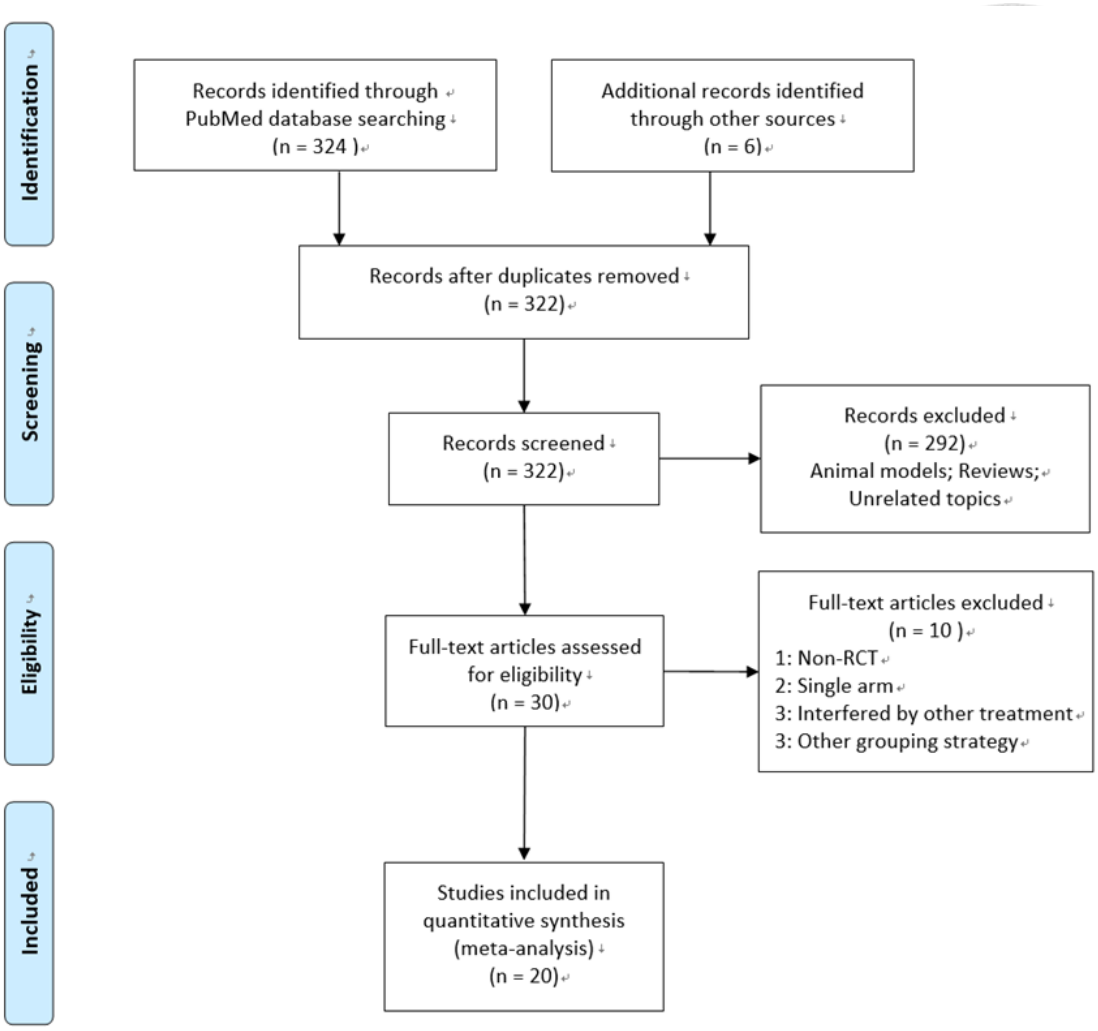

Figure 1. Flow chart of searching process: preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram

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Study	Country	Study type (RCT)	Control(n)	Treatment 1 (n)	Treatment 2 (n)	Treatment 3 (n)	Treatment duration	Follow-up duration	% female
Irani 2004[17]	Iran	double-blinded	50ml N/S (15)	120mg BCG (15)			6 weekly	24 months	100
Mayer 2005[22]	USA	double-blinded	50ml N/S (134)	50mg BCG (131)			6-10 weekly	24-28 weeks	81.9
Peters 1997[26]	USA	double-blinded	50ml N/S (15)	50mg BCG (15)			6 weekly	6 months	100
Propert 2008[44]	USA	double-blinded	50ml N/S (11)	50mg BCG (21)			6-10 weekly	68 weeks	80
El-Bahnasy 2009[45]	Egypt	double-blinded	no control	50mg BCG (18)	BTX-A 300U (18)		6 weekly	22-23 weeks	100
Sairanen 2009[46]	Finland	Open-label	no control	50ml BCG (38)	50ml 50% DMSO (37)		6 weekly	3 months	94.7
Pinto 2018[47]	Portugal	double-blinded	10 ml N/S (9)	OnaBotA 100U (10)			Once	12 weeks	100
Kuo 2009[48]	Taiwan	double-blinded	N/S (23)	BoNTA 200U (15)	BoNTA 100U (29)		Once	3 months	83.6
Kuo 2016[49]	Taiwan	double-blinded	N/S (20)	BTX (40)			Once	8 weeks	86.7
Manning 2013[21]	Australia	double-blinded	N/S (27)	AboBTX 200U (=Botox 100U) (26)			Once	3 months	100
Nickel 2010[50]	Canada	double-blinded	20ml N/S (32)	20 ml CS (33)			6 weekly	12 weeks	98.4
Nickel 2012[41]	Canada	double-blinded	20ml N/S (49)	20 ml CS (49)			7 weekly	11 weeks	100
Tutolo 2017[29]	Belgium, Italy	double-blinded	50ml DMSO 50% (14)	20 ml CS 2% (22)			6 weekly	18 weeks	86.1
Shao 2010[40]	China	Open-label	N/S (11)	40 mg HA (20)	Heparin 12500 U + Lidocaine 100mg(16)		4 weekly, then 2 monthly	3 months	100
Cervigni 2017[51]	Italy	Open-label	No control	DMSO (36)	HA+CS (74)		13 weekly	6 months	100
Nickel 2009[23]	Canada	double-blinded	10 ml N/S (52)	10 ml (200mg) Lidocaine (50)			5 daily	29 days	97.1
Chen 2005[30]	Canada	double-blinded	N/S (4)	0.05 uM RTX (8)	0.10 uM RTX (10)		Once	12 weeks	77.3
Payne 2005[52]	USA	double-blinded	placebo (44)	0.05 uM RTX (41)	0.10 uM RTX (35)	0.01 uM RTX (43)	Once	4 weeks	85.9
Gulpinar 2014[53]	Turkey	double-blinded	No control	HA (120 mg HA in 50 mL)	HA (800 mg/50 mL) + CS (1 g/50 mL)		4 weekly then 2 bi-weekly, followed by 2 monthly	6 months	100
Gulpinar 2018[54]	Turkey	double-blinded	No control	40 ml CS (21)	80 ml HA (21)		4 weekly then 2 bi-weekly, followed by 2 monthly	6 months	100

Table 1. The general characteristics of the included twenty studies

RCT: randomized controlled trial; N/S: normal saline; BCG: Bacillus Calmette-Guerin; BTX: Botulinum toxin; BoNTA: Botulinum neurotoxin A; CS: Chondroitin sulfate; HA: hyaluronic acid; DMSO: Dimethyl sulfoxide; RTX: Resiniferatoxi

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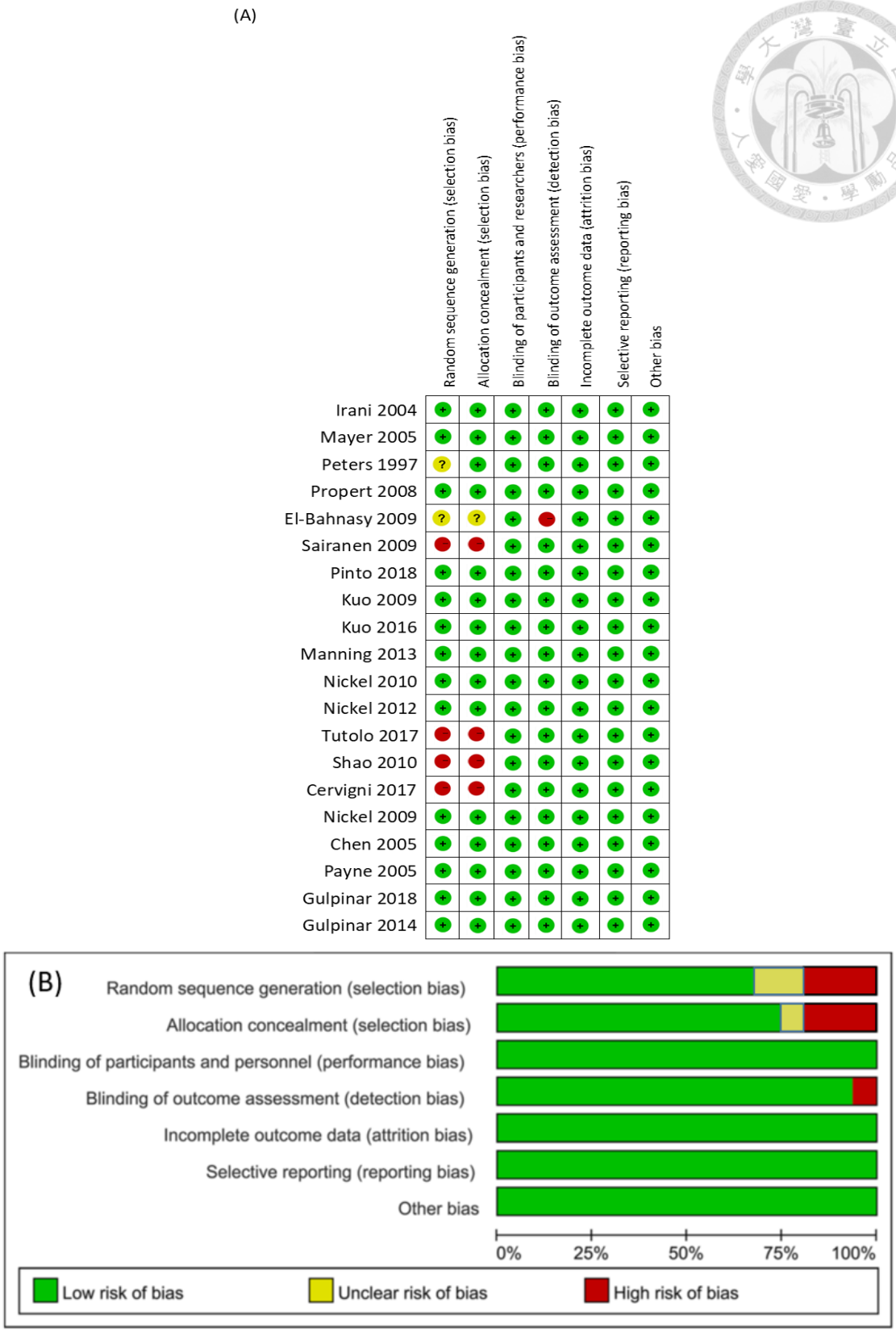

Figure 2. Risk of bias graph and summary of the included studies: (A) reviewers' judgements about each risk of bias item for eligible studies and (B) the judgements about each risk of bias item presented as percentages across all eligible studies

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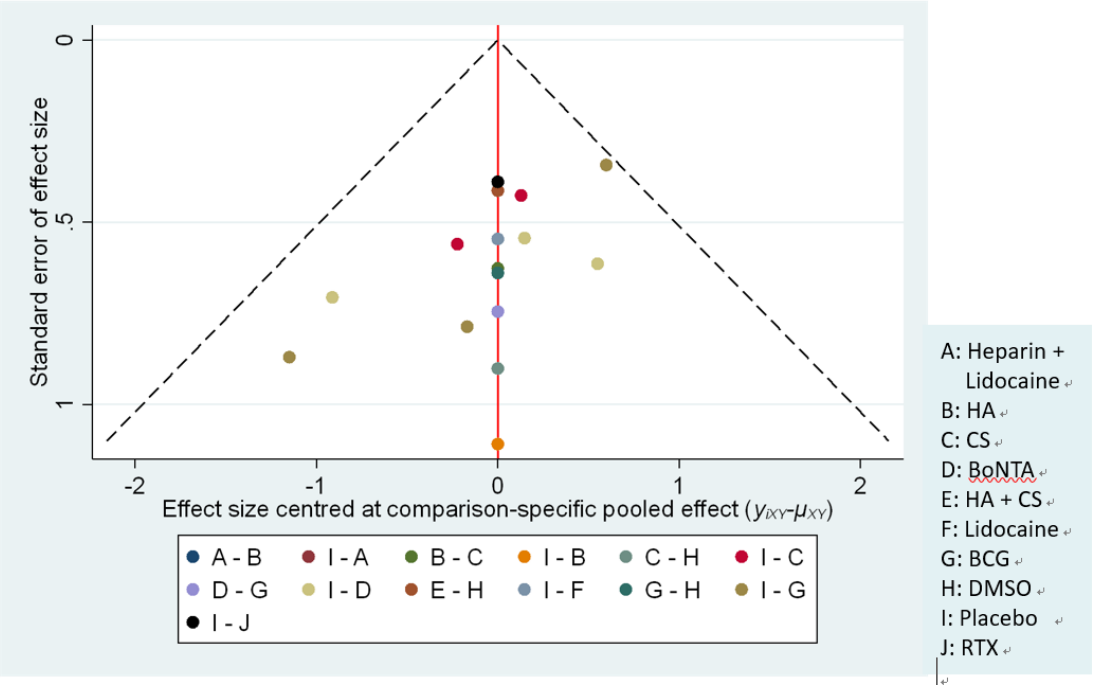

Figure 3. Funnel plots on global response assessment (GRA)
Little evidence of publication bias was demonstrated by visual or statistical examination of the funnel plots.

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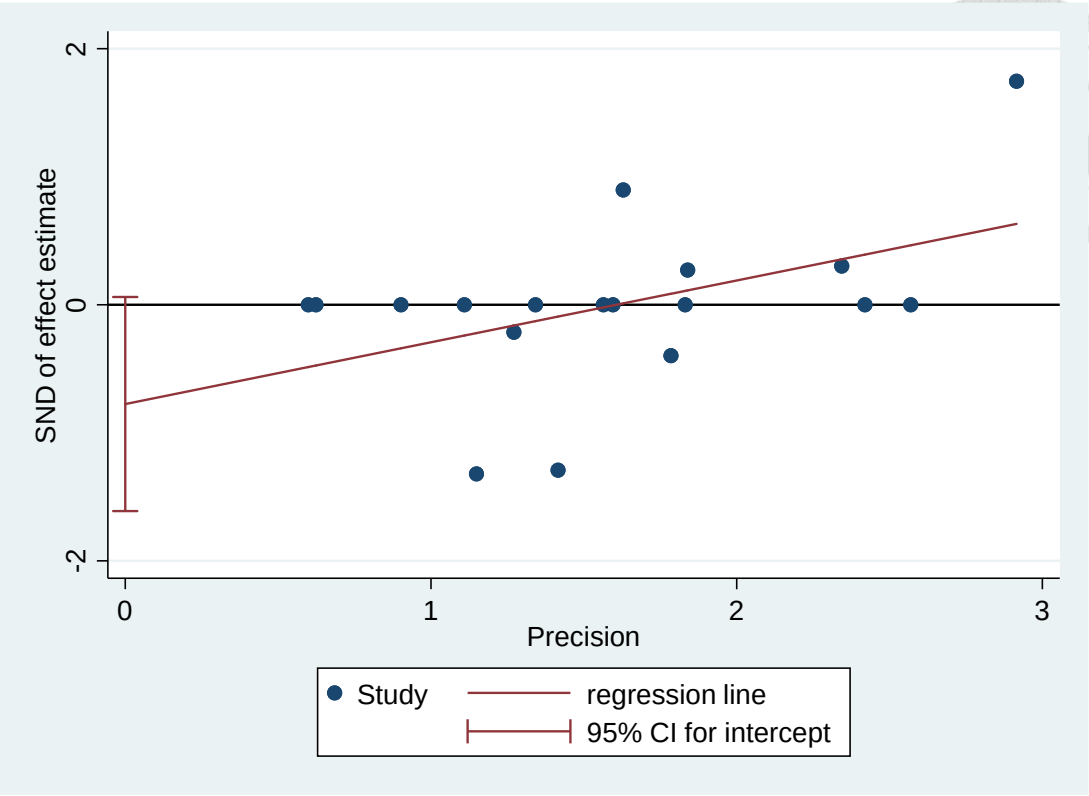

Figure 4 Egger's test for small study effects on global response assessment (GRA)

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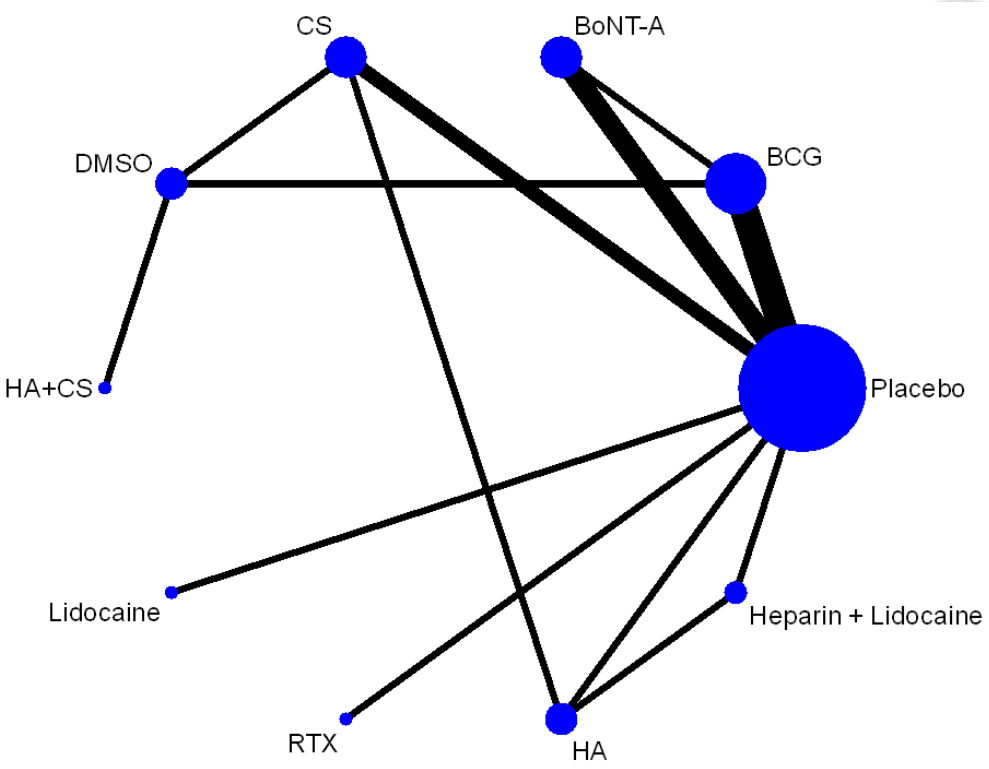

Figure 5. Network map of eligible comparisons for global response assessment (GRA)

doi:10.6342/NTU201803031

Placebo	2.24 (0.76,6.61)	4.18 (1.23,14.17)	5.13 (1.28,20.48)	1.95 (0.27,14.30)	2.72 (0.14,51.83)	2.42 (0.25,23.77)	0.66 (0.08,5.70)	8.30 (1.05,65.53)	55.23 (1.50,2032.91)
	BCG	1.87 (0.44,8.01)	2.29 (0.44,11.94)	0.87 (0.13,5.95)	1.21 (0.07,22.07)	1.08 (0.09,13.54)	0.29 (0.03,3.29)	3.71 (0.38,36.16)	24.67 (0.58,1049.28)
		BoNTA	1.23 (0.20,7.57)	0.47 (0.05,4.49)	0.65 (0.03,14.99)	0.58 (0.04,7.72)	0.16 (0.01,1.88)	1.99 (0.18,21.52)	13.21 (0.29,591.93)
			CS	0.38 (0.05,2.87)	0.53 (0.03,10.31)	0.47 (0.03,6.83)	0.13 (0.01,1.67)	1.62 (0.24,11.13)	10.77 (0.26,443.83)
				DMSO	1.39 (0.16,12.25)	1.24 (0.06,25.70)	0.34 (0.02,6.37)	4.26 (0.29,61.68)	28.31 (0.49,1639.30)
					HA+CS	0.89 (0.02,37.14)	0.24 (0.01,9.37)	3.06 (0.10,95.90)	20.33 (0.20,2031.63)
						Lidocaine	0.27 (0.01,6.30)	3.43 (0.16,74.60)	22.81 (0.32,1628.76)
							RTX	12.59 (0.64,249.65)	83.76 (1.25,5596.02)
								HA	6.65 (0.17,260.42)
									Heparin+Lidocaine

Table 2. The network meta-analysis results of global response assessment (GRA) for different treatment comparisons. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; DMSO, Dimethyl sulfoxide; HA+CS, hyaluronic acid + Chondroitin sulfate; RTX, Resiniferatoxin; HA, hyaluronic acid

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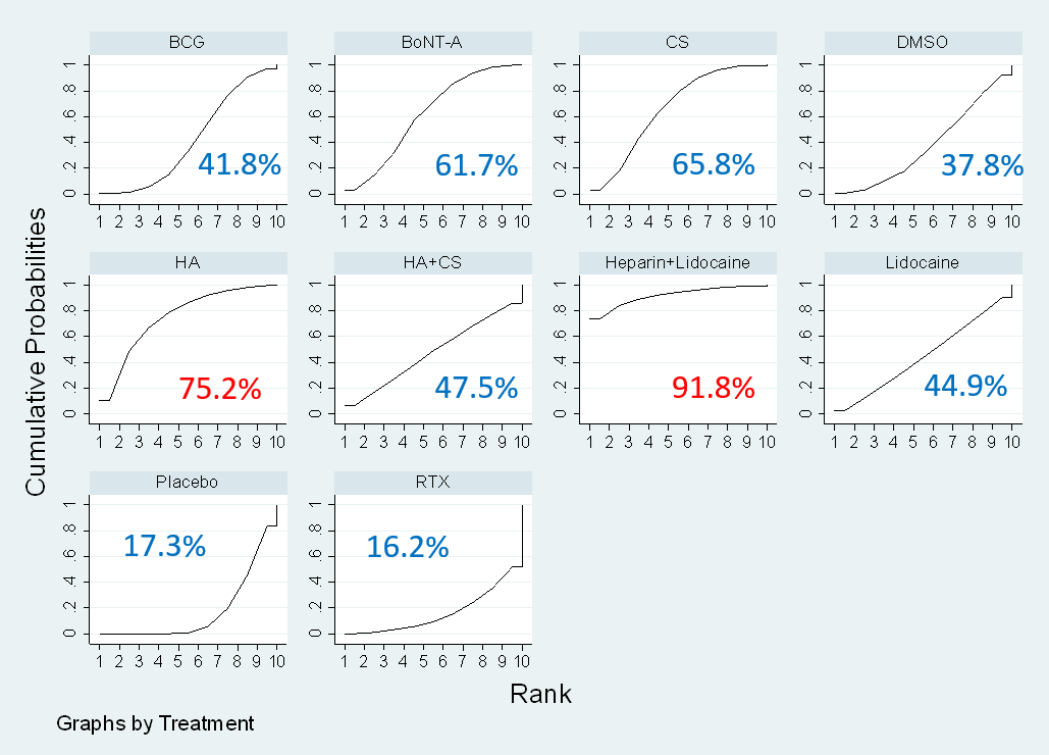

Figure 6. SUCRA ranking for cumulative probability of the global response assessment (GRA)

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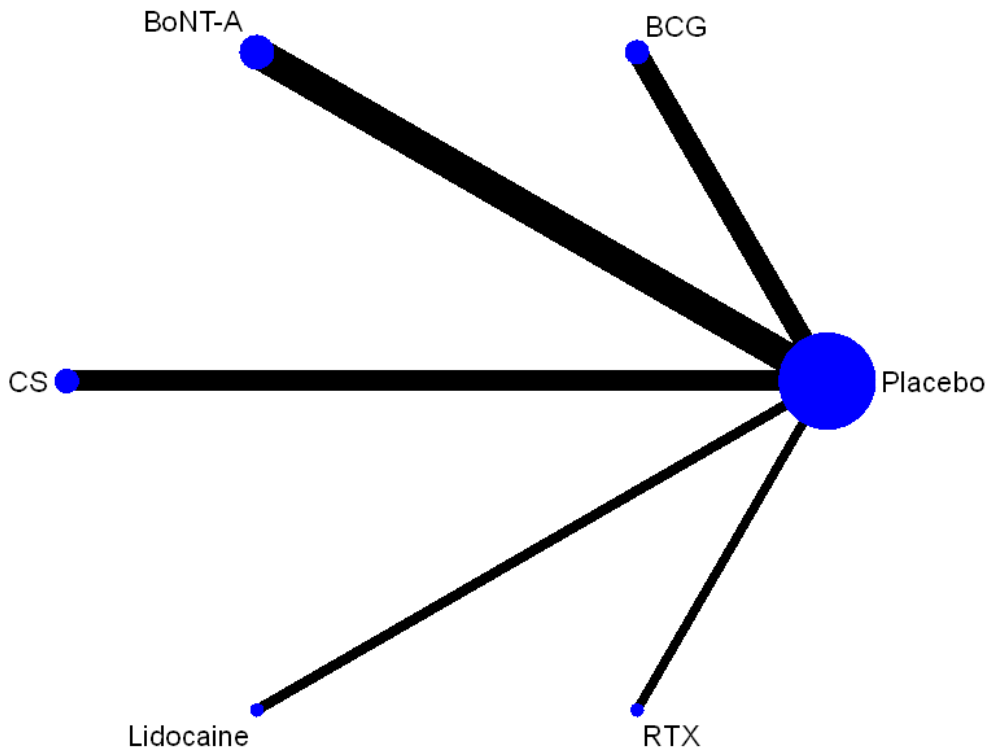

Figure 7. Network map of eligible comparisons for O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI)

doi:10.6342/NTU201803031

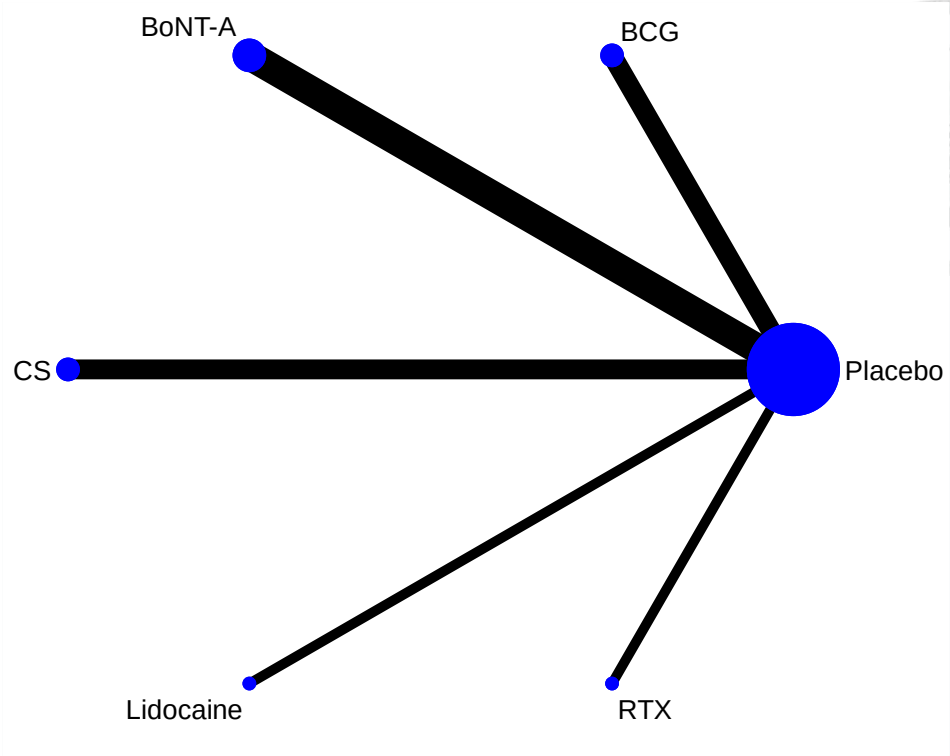

Figure 8. Network map of eligible comparisons for O'Leary-Sant Interstitial Cystitis Problem Index (ICPI)

doi:10.6342/NTU201803031

Placebo	-0.59 (-1.48,0.3)	-1.18 (-1.69,-0.66)	0.23 (-1.13,1.59)	-1.33 (-2.76,0.10)	-2.33 (-5.16,0.69)
	BCG	-0.59 (-1.62,0.44)	0.82 (-0.81,2.44)	-0.74 (-2.43,0.95)	-1.64 (-4.70,1.41)
		BoNTA	1.40 (-0.05,2.86)	-0.15 (-1.68,1.37)	-1.06 (-4.03,1.91)
			CS	-1.56 (-3.53,0.42)	-2.46 (-5.69,0.76)
				Lidocaine	-0.90 (-4.16,2.35)
					RTX

Table 3 The network meta-analysis results of O'Leary-Sant Interstitial Cystitis Symptom Index (ICSI) for different treatment comparisons. The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; RTX, Resiniferatoxin.

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Placebo	-0.57 (-1.42,0.28)	-2.58 (-3.04,-2.11)	0.61 (-0.54,1.75)	-1.63 (-3.03,-0.23)	-3.10 (-6.63,0.44)
	BCG	-2.01 (-2.98,-1.03)	1.18 (-0.25,2.60)	-1.06 (-2.70,0.58)	-2.53 (-6.16,1.11)
		BoNTA	3.18 (1.95,4,42)	0.95 (-0.53,2.42)	-0.52 (-4.08,3.04)
			CS	-2.24 (-4.04,-0.43)	-3.7 (-7.42,0.01)
				Lidocaine	-1.47 (-5.27,2.34)
					RTX

Table 4. The network meta-analysis results of O'Leary-Sant Interstitial Cystitis Problem Index (ICPI) for different treatment comparisons. The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; RTX, Resiniferatoxin.

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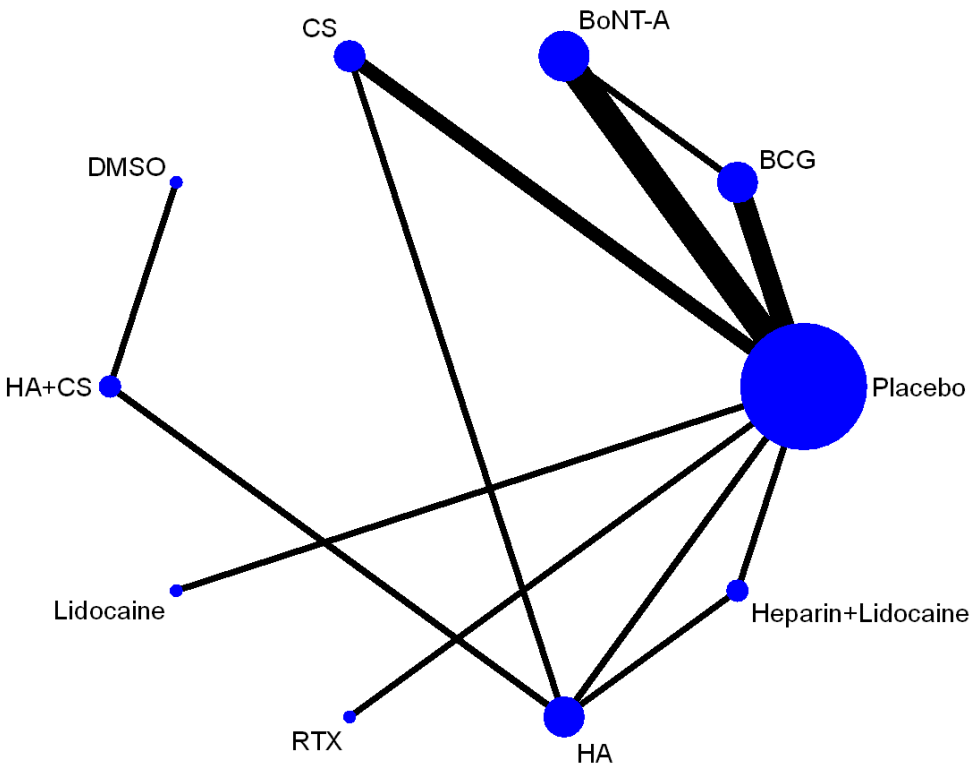

Figure 9. Network map of eligible comparisons for frequency

doi:10.6342/NTU201803031

Placebo	-0.83 (-4.47,2.82)	-3.34 (-6.55,-0.14)	-1.75 (-6.02,2.52)	-3.7 (-14.92,7.52)	-3.31 (-12.31,5.68)	-1.91 (-8.83,5.01)	-2.50 (-10.32,5.31)	-3.22(-8.55,2.12)	-5.14 (-11.72,1.44)
	BCG	-2.52 (-6.74,1.71)	-0.92 (-6.53,4.69)	-2.88 (-14.67,8.92)	-2.49 (-12.19,7.22)	-1.08 (-8.91,6.74)	-1.68 (-10.30,6.95)	-2.39 (-8.85,4.07)	-4.31 (-11.83,3.21)
		BoNT-A	1.59 (-3.74,6.93)	-0.36 (-12.03,11.31)	0.03 (-9.52,9.58)	1.43 (-6.19,9.06)	0.84 (-7.61,9.29)	0.13 (-6.10,6.35)	-1.79 (-9.11,5.52)
			CS	-1.95 (-13.21,9.31)	-1.56 (-10.61,7.48)	-0.16 (-8.29,7.97)	-0.76 (-9.66,8.15)	-1.47 (-6.89,3.95)	-3.39 (-10.68,3.90)
				DMSO	0.39 (-6.32,7.10)	1.79 (-11.39,14.98)	1.20 (-12.48,14.87)	0.48 (-9.39,10.36)	-1.44 (-13.34,10.47)
					HA+CS	1.40 (-9.95,12.75)	0.81 (-11.11,12.73)	0.10 (-7.15,7.34)	-1.83 (-11.66,8.01)
						Lidocaine	-0.59 (-11.04,9.85)	-1.31 (-10.05,7.43)	-3.23 (-12.78,6.32)
							RTX	-0.71 (-10.18,8.75)	-2.63 (-12.85,7.58)
								HA	-1.92 (-8.57,4.72)
									Heparin+Lidocaine

Table 5. The network meta-analysis results of frequency for different treatment comparisons.
The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; DMSO, Dimethyl sulfoxide; HA+CS, hyaluronic acid + Chondroitin sulfate; RTX, Resiniferatoxin; HA, hyaluronic acid

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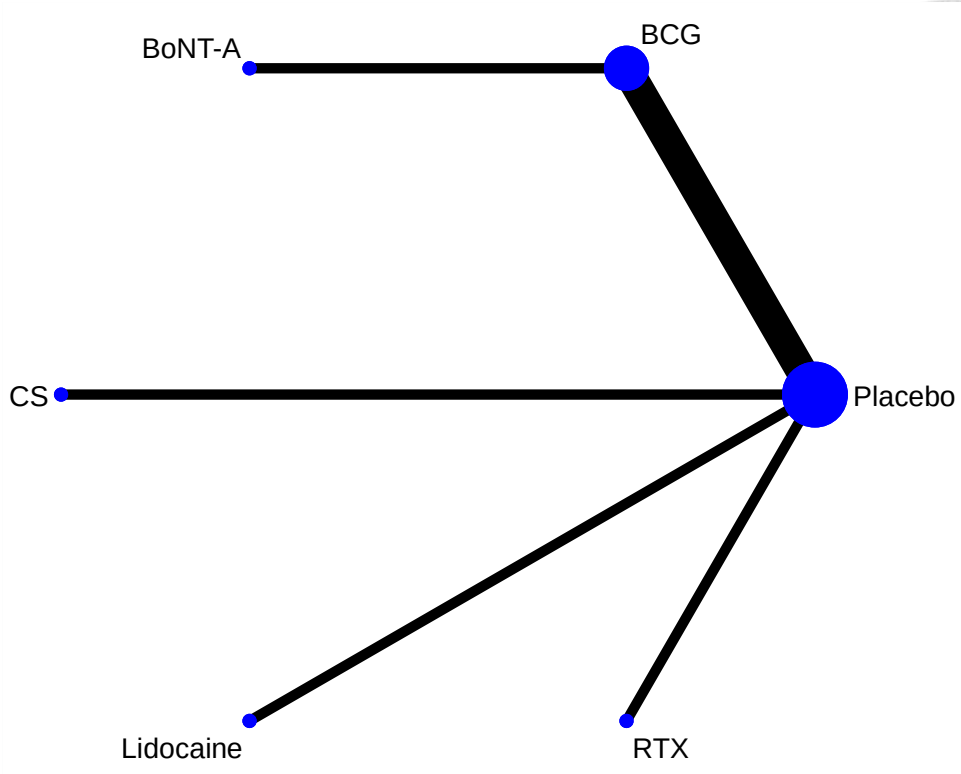

Figure 10. Network map of eligible comparisons for urgency

doi:10.6342/NTU201803031

Placebo	-0.65 (-1.08,-0.22)	-2.48 (-3.31,-1.66)	0.00 (-1.80,1.80)	-0.82 (-1.67,0.03)	-2.13 (-6.72,2.45)
	BCG	-1.83 (-2.53,-1.13)	0.65 (-1.20,2.50)	-0.17 (-1.12,0.78)	-1.48 (-6.09,3.12)
		BoNTA	2.48 (0.51,4.46)	1.66 (0.48,2.85)	0.35 (-4.30,5.01)
			CS	-0.82 (-2.81,1.17)	-2.13 (-7.06,2.79)
				Lidocaine	-1.31 (-5.97,3.35)
					RTX

Table 6. The network meta-analysis results of urgency for different treatment comparisons.
The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment.
A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant.
BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; RTX, Resiniferatoxin

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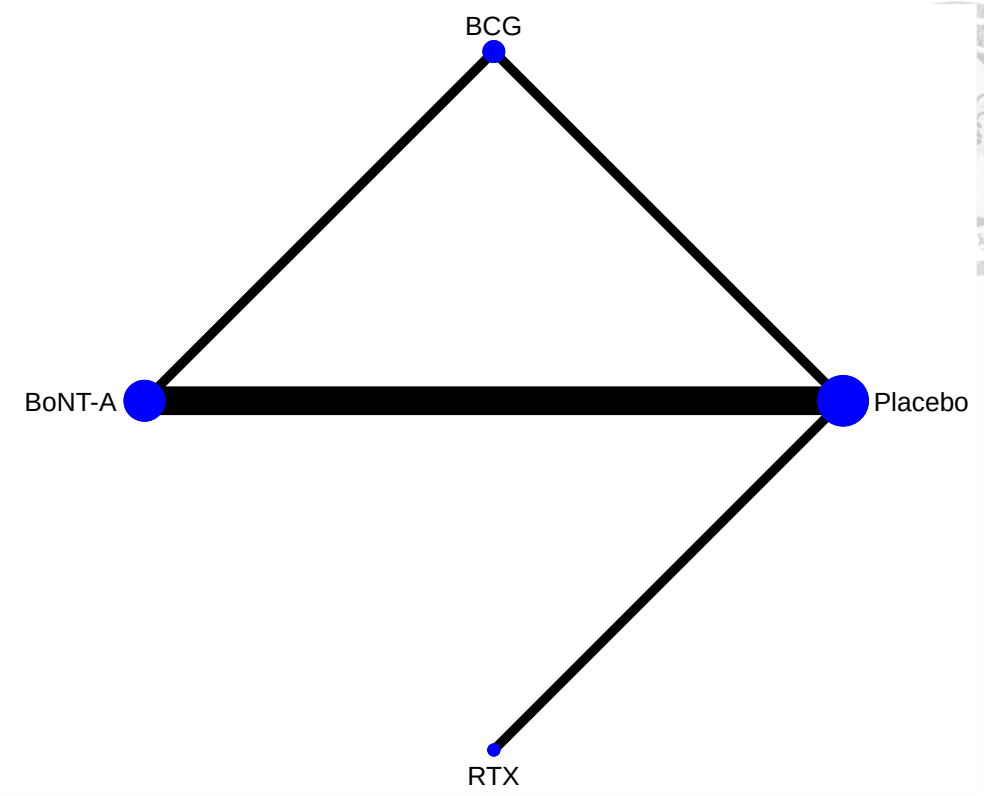

Figure 11. Network map of eligible comparisons for nocturia

doi:10.6342/NTU201803031

Placebo	-0.41 (-2.72,1.90)	-0.83 (-2.31,0.66)	-1.77 (-5.38,2.28)
	BCG	-0.42 (-2.98,2.15)	-1.37 (-6.03,3.30)
		BoNTA	-0.95 (-5.27,3.37)
			RTX

Table 7. The network meta-analysis results of nocturia for different treatment comparisons.
The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment.
A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant.
BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; RTX, Resiniferatoxin

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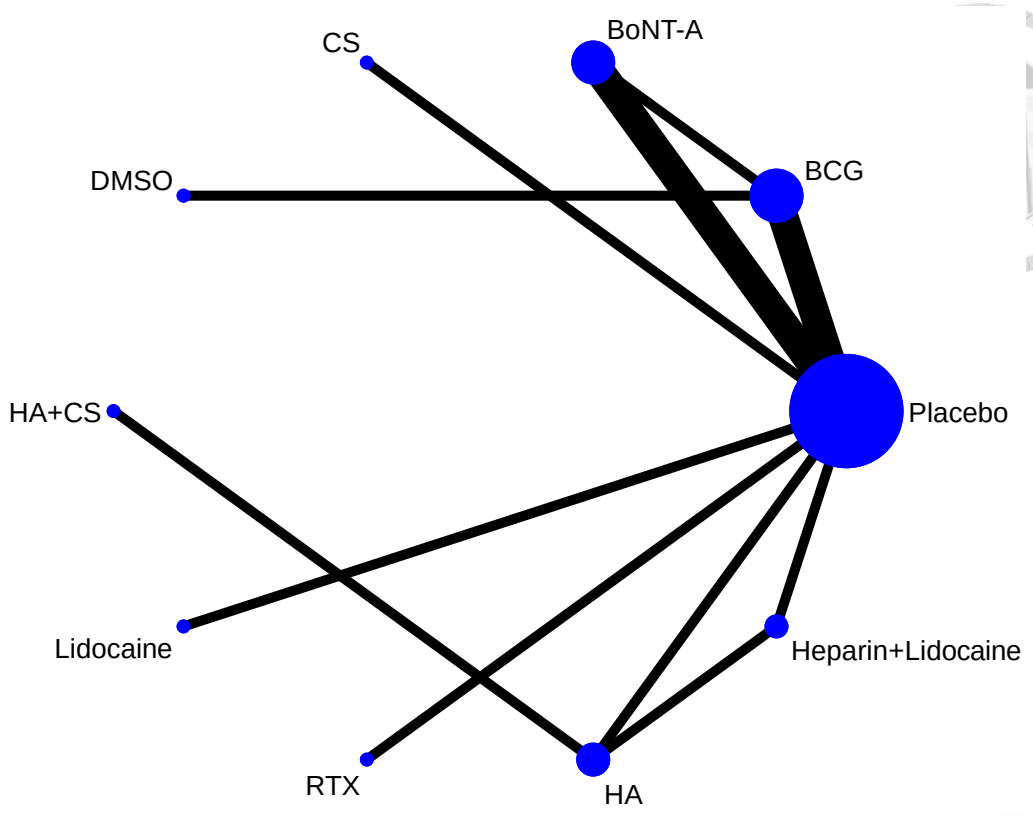

Figure 12. Network map of eligible comparisons for visual analogue scale for pain (VAS)

doi:10.6342/NTU201803031

Placebo	-0.92 (-1.7,-0.14)	-1.88 (-2.80,-0.96)	0.4 (-1.10,1.90)	-1.92 (-3.64,-0.20)	-3.40 (-5.91,-0.88)	-0.82 (-2.38,0.74)	0.53 (-2.23,3.28)	-3.60 (-5.36,-1.84)	-3.20 (-5.00,-1.39)
	BCG	-0.96 (-1.96,0.04)	1.32 (-0.37,3.01)	-1.00 (-2.53,0.53)	-2.48 (-5.11,0.15)	0.10 (-1.64,1.84)	1.45 (-1.41,4.31)	-2.68 (-4.61,-0.75)	-2.28 (-4.25,-0.31)
		BoNT-A	2.28 (0.52,4.04)	-0.04 (-1.87,1.79)	-1.52 (-4.20,1.16)	1.06 (-0.75,2.87)	2.41 (-0.50,5.31)	-1.72 (-3.71,0.27)	-1.32 (-3.35,0.71)
			CS	-2.32 (-4.60,-0.04)	-3.80 (-6.73,-0.87)	-1.22 (-3.38,0.94)	0.13 (-3.01,3.26)	-4.00 (-6.31,-1.69)	-3.6 (-5.95,-1.25)
				DMSO	-1.48 (-4.52,1.56)	1.10 (-1.22,3.42)	2.45 (-0.80,5.69)	-1.68 (-4.14,0.78)	-1.28 (-3.77,1.21)
					HA+CS	2.58 (-0.38,5.54)	3.93 (0.20,7.66)	-0.20 (-1.99,1.59)	0.20 (-2.12,2.51)
						Lidocaine	1.35 (-1.82,4.51)	-2.78 (-5.13,-0.43)	-2.38 (-4.76,0.00)
							RTX	-4.13 (-7.40,-0.86)	-3.73 (-7.02,-0.43)
								HA	0.40 (-1.06,1.86)
									Heparin+Lidocaine

Table 8. The network meta-analysis results of visual analogue scale for pain (VAS) for different treatment comparisons.
The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference below zero favors the column-defining treatment. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; CS, Chondroitin sulfate; DMSO, Dimethyl sulfoxide; HA+CS, hyaluronic acid + Chondroitin sulfate; RTX, Resiniferatoxin; HA, hyaluronic acid

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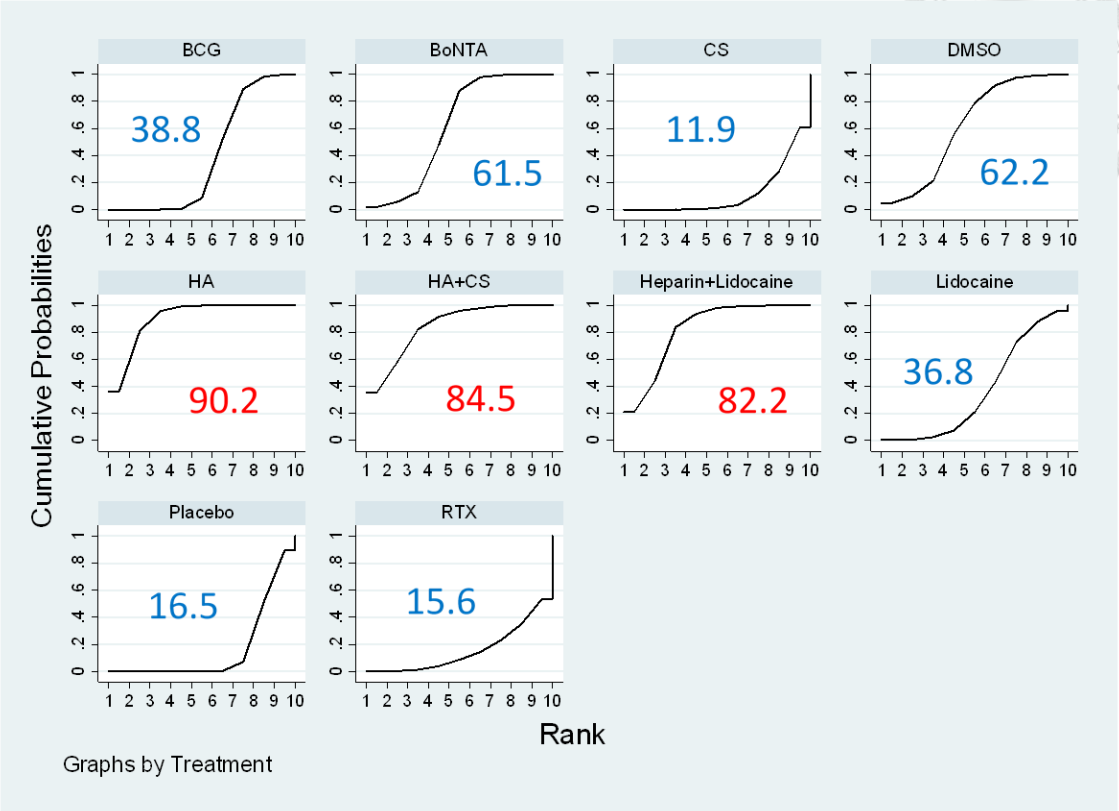

Figure 13. SUCRA ranking for cumulative probability of the visual analogue scale for pain (VAS)

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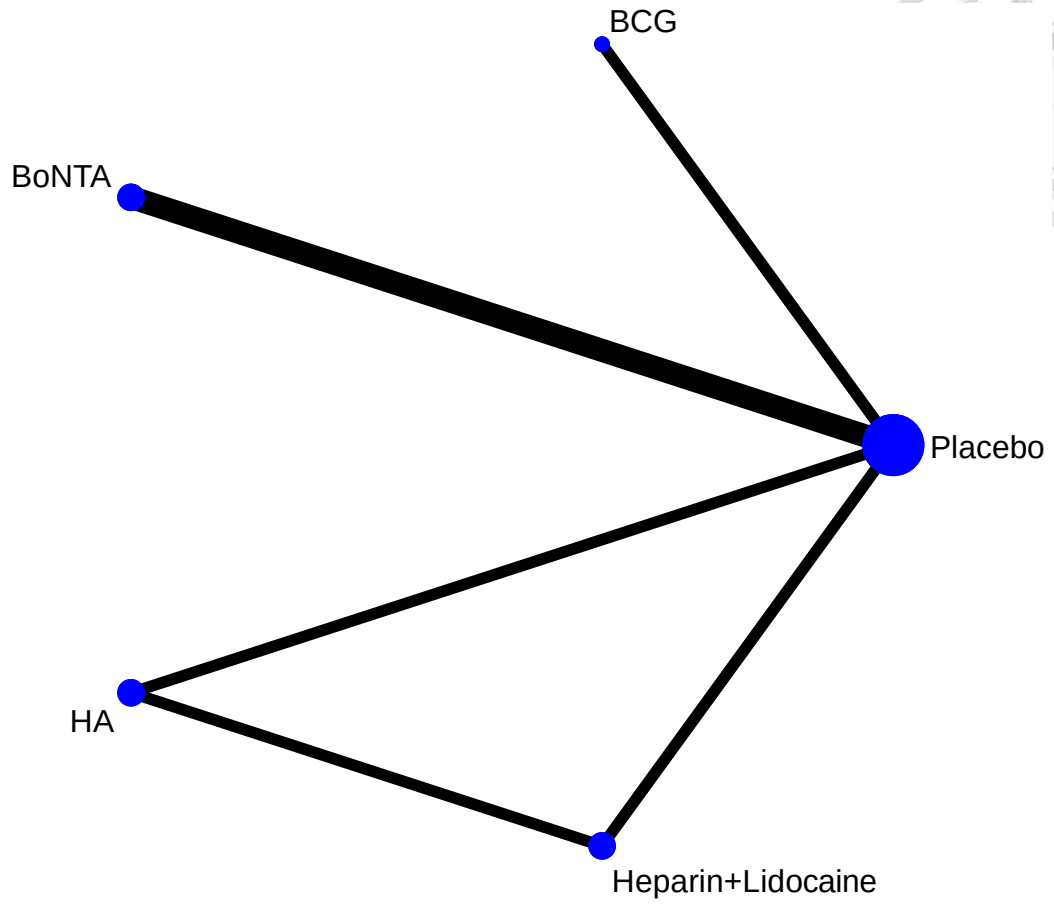

Figure 14. Network map of eligible comparisons for functional bladder capacity (FBC)

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Placebo	-9.00 (-41.76,23.76)	22.40 (-10.38,55.19)	57.50 (46.90,68.10)	55.50 (43.33,67.56)
	BCG	31.40 (-14.95,77.75)	66.50 (32.07,100.93)	64.50 (29.59,99.41)
		BoNTA	35.10 (0.64,69.55)	33.10 (-1.83,68.03)
			HA	-2.00 (-15.11,11.11)
				Heparin+Lidocaine

Table 9. The network meta-analysis results of functional bladder capacity (FBC) for different treatment comparisons.
The efficacy estimate is located at the intersection of the column-defining treatment and the row-defining treatment. A mean difference "above" zero favors the column-defining treatment. Underlined results are statistically significant. BCG, Bacillus Calmette-Guerin; BoNTA, Botulinum neurotoxin A; HA, hyaluronic acid

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```
Testing for inconsistency:
 ( 1)  [_y_C]des_BC = 0
 ( 2)  [_y_I]des_DI = 0

           chi2(  2) =   71.84
         Prob > chi2 =    0.0000
mvmeta command stored as F9; test command stored as F8

. network sidesplit all, tau
```

Side	Direct		Indirect		Difference			tau
	Coef.	Std. Err.	Coef.	Std. Err.	Coef.	Std. Err.	P>|z|	
A B	-2.303292	1.941981	4.117694	3.501136	-6.420986	4.003453	0.109	2.975648
A C	-2.272296	1.63126	-8.69322	3.656252	6.420924	4.003446	0.109	2.975646
A D	.6010643	1.508836	-11.96993	3.336849	12.57099	3.662123	0.001	1.967792
A G	.	.	.	.	.	.	.	.
A H	.	.	.	.	.	.	.	.
A I *	-8.1	2.23525	4.471024	2.900824	-12.57102	3.66212	0.001	1.967792
A J *	-7.5	2.291253	17.64205	7.049494	-25.14205	7.324239	0.001	1.967792
B C	-6.39	3.097908	.0309943	2.535882	-6.420994	4.003465	0.109	2.97565
D I	3.87	2.477554	-8.701023	2.696832	12.57102	3.662127	0.001	1.967792
E F *	.39	3.426365	-6.518699	2430.852	6.908699	2430.854	0.998	3.314443
F I *	.0999999	3.700122	-3.644379	1157.892	3.744379	1157.898	0.997	3.314447
I J *	.6	2.37628	-24.54205	6.964536	25.14205	7.324239	0.001	1.967792

Figure S1. Testing for inconsistency

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