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ORIGINAL ARTICLE

Comparative effectiveness of interventions for managing postoperative catheter-related bladder discomfort: a systematic review and network meta-analysis

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Abstract

Background Although many drugs or interventions have been studied to manage catheter-related bladder discomfort (CRBD), their comparative effectiveness is unknown. We attempted to assess the comparative effectiveness of the strategies to manage CRBD in patients undergoing urologic surgery including amikacin, solifenacin, darifenacin, butylscopolamine, dexmedetomidine, gabapentin, glycopyrrolate, ketamine, oxybutynin, resiniferatoxin, tolterodine, tramadol, caudal block, dorsal penile nerve block, lidocaine–prilocaine cream.

Methods We performed an arm-based network meta-analysis including 29 trials with 2841 participants. Goodness of model fit was evaluated by deviance information criteria (DIC). The incidence of CRBD at 0, 1, and 6 h after surgery and the incidence of moderate to severe CRBD at 0, 1, and 6 h after surgery were compared.

Results Random effect model was selected according to DIC. Most of the drugs significantly decreased the incidence of CRBD except amikacin, tramadol at 0 and 1 h after surgery. Dexmedetomidine, solifenacin, caudal block, dorsal penile nerve block, resiniferatoxin, and gabapentin 1200 mg p.o. significantly decreased the incidence of CRBD at 6 h after surgery (gabapentin 1200: Odds ratio [OR] 0.02; SUCRA 95.6). Dexmedetomidine and tolterodine significantly decreased the incidence of moderate to severe CRBD at 0, 1, and 6 h after surgery (tolterodine at 6 h: OR 0.05; SUCRA 73.7).

Conclusions Gabapentin was ranked best regarding the overall incidence of CRBD, while tolterodine was ranked best in reducing the severity of CRBD. However, a firm conclusion cannot be made from our analysis due to small-study number and heterogeneity regarding study setting and outcome measurement.

Keywords Catheter-related bladder discomfort · Network · Meta-analysis · Gabapentin · Tolterodine

Introduction

Catheter-related bladder discomfort (CRBD) due to an indwelling urinary catheter results in significant postoperative distress when patients awake from anesthesia. Patients describe CRBD as discomfort in the suprapubic area caused by irritation of bladder due to a catheter or a burning sensation with an urge to void [1]. Since CRBD may exacerbate postoperative pain and reduce the quality of life, there is a need to investigate any drug or intervention that could decrease the incidence and severity of CRBD.

CRBD is considered to be associated with muscarinic receptors, particularly subtype 3 [1]. Many drugs which block this muscarinic receptor including butylscopolamine, tolterodine, oxybutynin, solifenacin, and glycopyrrolate were investigated to prevent or treat CRBD [1–5]. A central

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α_2-adrenoceptor agonist, dexmedetomidine has recently been studied with favorable results [6]. However, drugs controlling other mechanisms including amikacin as an aminoglycoside antibiotic [7], and gabapentin and tramadol as an anti-nociceptive drug [8], were also investigated. Peripheral nerve block including caudal block, dorsal penile block, and lidocaine–prilocaine cream was investigated and showed a beneficial effect [9, 10]. Anesthetics such as ketamine, sevoflurane, desflurane, and propofol were compared for their influence on postoperative CRBD [11].

Although several narrative or systemic reviews of these drugs and procedures have been published [12, 13], a head-to-head comparison of these interventions has rarely been performed. Therefore, although many drugs with the various mechanism of action were studied, little is known about their comparative effectiveness. As such, head-to-head comparison of the effectiveness of all interventions is required to review the current body of evidence and to guide further clinical trials.

A network meta-analysis is a statistical technique that enables the comparison of different drugs that have not been directly compared through head-to-head randomized controlled trials (RCT) [14–20]. Even without previous study results, a comparison between two drugs is possible through a third common comparator [14], with direct and indirect comparisons integrated to synchronously evaluate multiple interventions. In addition, it is possible to determine the relative superiority of any modality compared to other drugs according to the statistical inference and to estimate the relative ranking.

Therefore, the primary aim of our study was to compare the efficacy of drugs and interventions to prevent and treat CRBD after urologic surgery. For this purpose, we performed a comprehensive network meta-analysis of the RCTs evaluating the effect of drugs or interventions to prevent CRBD in the setting of urologic surgery.

Materials and methods

To compare the protective effect of any drugs or interventions to prevent or treat CRBD, this study was conducted according to the recommendations from the Cochrane Handbook for Systemic Reviews of Interventions and was reported according to the PRISMA extension statements for network meta-analysis (Supplemental Table S1) [21]. This study was registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO)(CRD42017073353).

Eligibility criteria and search strategy

We included only RCTs conducted in adult patient ≥ 18-year-old undergoing any kind of urologic surgery which places urinary catheter postoperatively and evaluating the effects of any of the following drugs or interventions used preoperatively and/or intraoperatively: amikacin, dexmedetomidine, gabapentin, glycopyrrolate, butylscopolamine, ketamine, oxybutynin, resiniferatoxin, solifenacin, darifenacin, tolterodine, tramadol, dorsal penile block, lidocaine–prilocaine cream, and pudendal nerve block. The list of drugs included in our analysis was determined according to the following criteria: (1) there are at least one RCTs comparing the drug with a placebo control or other interventions among our included interventions and (2) reporting the incidence or severity of postoperative CRBD at least one of the following time frame: 0, 1, and 6 h after the surgery. Studies evaluating the therapeutic efficacy of an intervention in patients who developed CRBD were also included, however, only data regarding severity of CRBD were used in our network meta-analysis. The effect of gabapentin 600 mg and 1200 mg p.o. were compared in two previous studies, and there was a significant difference in the incidence of CRBD between the two dose groups [22]. The dose of the other drugs used in the included studies of our network did not differ significantly. Therefore, we decided to evaluate these two dose groups of gabapentin separately in our analysis. We could find a previous network meta-analysis which treated different dose groups of a single drug as different groups of the network [23].

Two authors (MH, WHK) independently searched Medline via PubMed interface, Embase databases, and Cochrane Central Register of Controlled Trials [Central, Issue 7 of 2017] from inception to July 2017. The same authors independently reviewed the titles and abstracts of all searched studies to identify eligible trials. The search strategy for PubMed, Embase, and Cochrane central registry is shown in the Supplemental Text S1. An additional search was performed by a bibliographic search of the trials included in our meta-analysis or previous meta-analysis. Our search was updated in July 2018 during the manuscript revision.

Data extraction and management

Data were independently extracted from the included studies by the two authors (MH, WHK) using a uniform data extraction form developed by the authors. Any discrepancies were resolved through a consensus discussion. The following information was extracted from each trial: the first author of the trial, location of the study, year of publication, the number of enrolled patients, inclusion and exclusion criteria, and distribution of outcome data.

Outcome definitions

The pre-specified primary endpoint was the incidence of postoperative CRBD in the recovery room at 1 h after

surgery. The secondary endpoint included the incidence of CRBD at 0 and 6 h after the arrival of the patients in the recovery room. The severity of CRBD at 0, 1, 6 h after the arrival of the patients in the recovery room, which was measured as mild, moderate, and severe, was also considered as secondary outcomes. Among the severity incidence, the incidences of moderate to severe CRBD at 0, 1, and 6 h after the surgery were compared. We changed the primary outcome to the incidence of CRBD at 1 h after surgery due to the largest sample size at this time point.

Statistical analysis

Data were analyzed using R version 3.4.1. (R Foundation for Statistical Computing), Stata/MP version 15.1 (StataCorp, College Station, Texas, USA), and Review Manager 5.3 (RevMan, The Cochrane Collaboration, Oxford, United Kingdom). For network meta-analysis, an arm-based random effect model was used to compare different pharmacologic interventions [24]. Along with the analysis of the direct within-trial comparisons between two interventions, the mixed technique comparison framework enabled incorporation of an indirect comparison of different agents. Model fit was measured by assessment of the posterior residual deviance and goodness of model fit was evaluated by comparing Dbar, leverage, and deviance information criterion (DIC) between random and fixed effect model [25]. We selected a random effect model according to the residual variance as well as DIC (Supplemental Table S2).

Pairwise associations between each modality were depicted by a graphical representation of the network. Network estimates from all outcome variables were presented as odds ratio [OR] with 95% credible intervals (CIs). Transitivity and consistency are the important assumptions of network meta-analysis related to the validity of indirect and mixed estimates [26]. The plausibility of transitivity assumption was evaluated based on the individual study characteristics. We assessed potentially important effect modifying covariates including patient age, sex, size of Foley catheter and duration of surgery.

Consistency within each closed triangle or quadratic loop was investigated using a loop-specific approach in the network meta-analysis. In all triangular and quadratic loop, the inconsistency factor of the ratio of two odds ratios (ROR) from direct and indirect evidence in the loop and its 95% confidence interval was estimated as the absolute difference between direct and indirect estimates for each comparison in the loop [27]. ROR value of 1 means that the two sources are in agreement and ROR values of two means that the difference between two estimates is double. We also evaluated heterogeneity for the indirect comparison analyses using τ^2, which examines between-study heterogeneity (smaller value indicates a better model).

To rank the treatments for an outcome, the comparative influence of individual agents to the incidence of CRBD was estimated from multidimensional scaling approach [15]. In addition, we calculated the surface under the cumulative ranking (SUCRA) probabilities for all outcomes [15]. SUCRA value is the percentage of efficacy or safety achieved by an agent compared to an imaginary agent that is always the best without uncertainty. A "comparison-adjusted" funnel plot was used to evaluate the presence of small-study effects in the network meta-analysis [28].

Risk of bias assessment

The risk of bias of individual studies was assessed using the bias domains described in the Cochrane Handbook for Systemic Reviews of Interventions, version 5.1.0 [29]. Two authors independently and subjectively reviewed all included studies and assigned a judgment of "high", "low", or "unclear" risk of bias across the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data and selective reporting (MH, WHK). Disagreements were resolved by discussion between the two assessors and a third outside assessor, who provided arbitration. We could not assess the quality of evidence because the consistency of any triangular loop could not be evaluated due to lack of indirect estimates [30].

The grades of recommendation, assessment, development and evaluation (GRADE) approach was used to rate the quality of evidence [30]. In this approach, we start the rating of direct evidence from RCTs at a high-quality and we can rate down based on the risk of bias, inconsistency, imprecision, and publication bias to levels of moderate, low and very low quality. Secondly, we start the rating of indirect estimates at the lowest rating of the two pairwise estimates that contribute as first-order loops to the indirect estimate, but we can rate down further for intransitivity or imprecision. Thirdly, if direct and indirect estimates were similar, we can assign the higher rating to the network meta-analysis estimates.

Results

Supplemental Figure S1 shows the search results and reasons for exclusion from the current study. We initially screened 1458 titles and performed an additional search from conference abstract or clinical trial registration website or reference list of included articles. Then we eliminated 362 duplicate studies and 1081 articles not meeting the inclusion criteria. After carefully reviewing the full text of the remaining 50 studies, 21 were excluded due to the reasons described in

Supplemental Figure S1. Finally, 29 RCTs were included (Supplemental Text S2).

Supplemental Table S1 shows the characteristics of studies included in the analysis. These 29 studies included 2841 patients and 16 interventions listed in methods. There was significant heterogeneity regarding sex ratio, age, type and duration of surgery and size of Foley catheter. Table 1 shows the number of included studies and enrolled patients according to the individual interventions. Although there was one RCT of pudendal nerve block [31], the time point reporting the incidence of CRBD in this study did not meet the time frame of our inclusion criteria. Additionally, we found one RCT reporting the effect of caudal block which met our inclusion criteria. Although caudal block was not planned in our study protocol, we included caudal block in our network meta-analysis. The numbers of studies and patients according to the different outcomes of the study are shown in Table 2.

Table 1 Number of included studies and enrolled patients according to the individual interventions

Interventions	Studies (*n*)	Intervention group (*n*)	Published year
Glycopyrrolate	2	77	2015–2016
Solifenacin	3	150	2014–2017
Tolterodine	4	234	2005–2018
Oxybutynin	3	123	2006–2009
Butylscopolamine	2	73	2015–2017
Dexmedetomidine	5	213	2015–2017
Amikacin	1	50	2016
Gabapentin 600 mg p.o	4	170	2007–2018
Gabapentin 1200 mg p.o	2	67	2012
Tramadol	2	54	2008–2016
Pudendal nerve block	0	–	–
Caudal block	1	24	2013
Dorsal penile nerve block	1	29	2016
Lidocaine–prilocaine cream	1	72	2017
Ketamine	3	107	2006–2016
Resiniferatoxin	1	24	2012
Darifenacin	1	30	2016
Control	28	1344	2005–2018
Total	29	2841	2005–2018

Figure 1 shows the geometry of the network for the overall incidence of CRBD and the incidence of moderate to severe CRBD at 0, 1 and 6 h after surgery. Figure 2 shows network estimates of each drug compared to placebo according to the six outcomes. Table 3, Supplemental Tables S2 and S3 show the network estimates of all possible pairs of drug comparison for all the outcomes.

Most of the drugs significantly decreased the incidence of CRBD at 0 and 1 h after surgery except amikacin, tramadol, caudal block, gabapentin 600 mg p.o. for 0 h after surgery and amikacin, tramadol, butylscopolamine for 1 h after surgery (Table 3). Dexmedetomidine, solifenacin, caudal block, dorsal penile nerve block, resiniferatoxin, and gabapentin significantly decreased the incidence of CRBD at 6 h after surgery (gabapentin 1200 mg p.o.: OR 0.02, 95% CI 0.00–0.09, SUCRA 95.6) (Supplemental Table S4). Regarding the severity of CRBD, dexmedetomidine and tolterodine significantly and consistently decreased the incidence of moderate to severe CRBD at 0, 1, and 6 h after surgery (tolterodine at 6 h after surgery: OR 0.05, 95% CI 0.02–0.18, SUCRA 73.7) (Supplemental Table S5). The adjusted SUCRA values of all interventions according to different outcomes were shown in Supplemental Table S6.

We ranked the comparative effectiveness of the interventions according to our six outcomes (Fig. 3). Supplemental Figure S2 shows the cumulative ranking plots of the interventions of the incidence of CRBD at 0 h. Gabapentin 1200 mg p.o. was ranked best regarding the overall incidence of CRBD at 0, 1, and 6 h after surgery. Tolterodine was ranked best regarding the incidence of moderate to severe CRBD. The comparison-adjusted funnel plot for assessing small-study effects regarding CRBD incidence at 1 h was depicted in Supplemental Figure S3. The funnel plot was not symmetrical, suggesting the source of small-study effects. The risk of bias of individual studies was shown in Supplemental Figure S4. Five studies were at low risk of bias and the remaining studies were at high or unclear risk of bias. The consistency plot of the incidence of CRBD at 1 h was shown in Supplemental Figure S5. The ROR from direct and indirect evidence in the loop shows large ROR with wide confidence interval, suggesting heterogeneity

Table 2 Number of included studies and enrolled patients according to the different outcomes

Outcomes	Incidence of CRBD at 0 h	Incidence of CRBD at 1 h	Incidence of CRBD at 6 h	Incidence of moderate to severe CRBD at 0 h	Incidence of moderate to severe CRBD at 1 h	Incidence of moderate to severe CRBD at 6 h	Total
Interventions	13	13	14	12	13	14	16
Studies (*n*)	20	23	17	15	16	15	29
Patients (*n*)	1878	2221	1737	1593	1952	1714	2841

CRBD catheter-related bladder discomfort

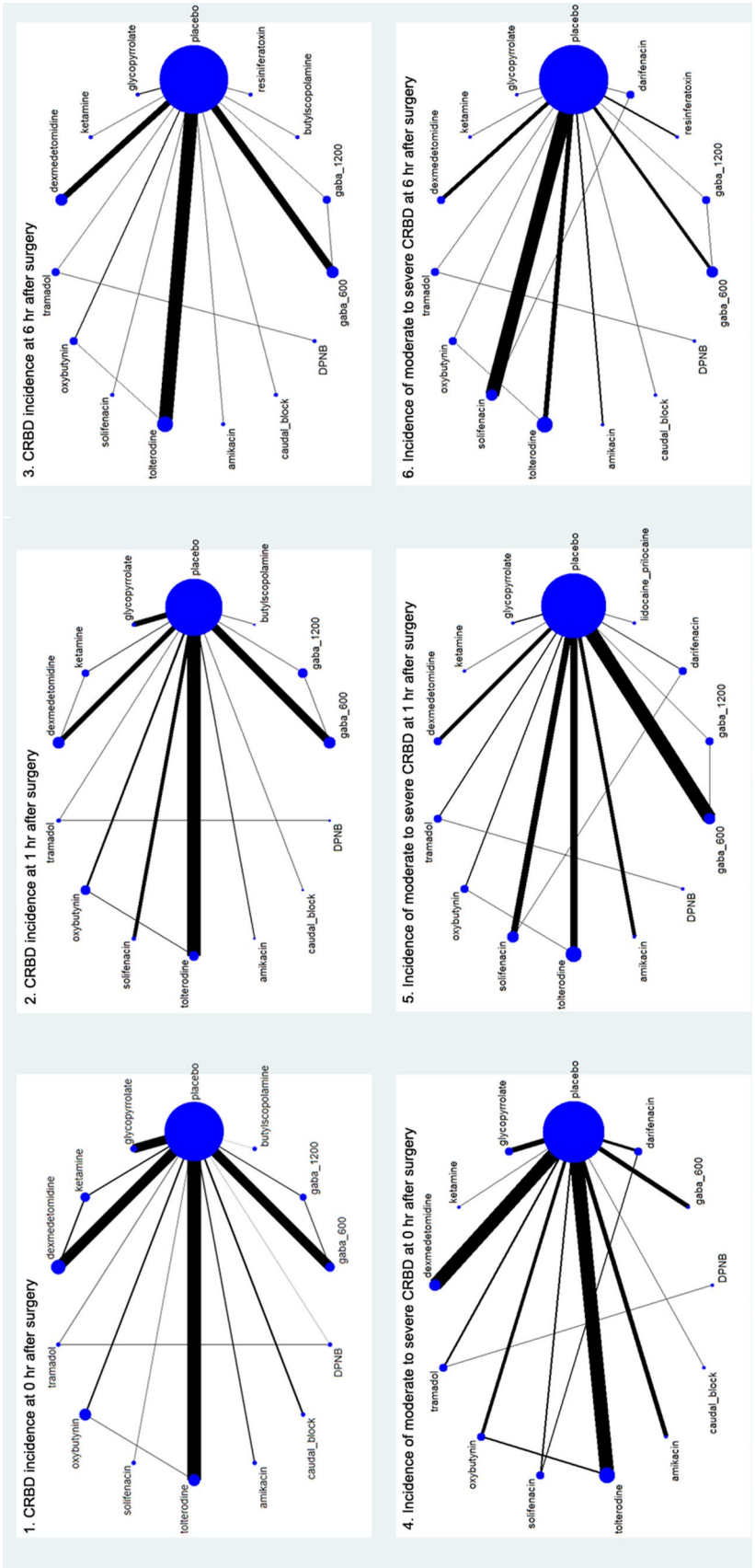

Fig. 1 Network plots of possible interventions according to our six outcomes. Nodes are weighted according to the number of patients with the respective interventions. Edges are weighted according to the number of studies between the two connected modalities

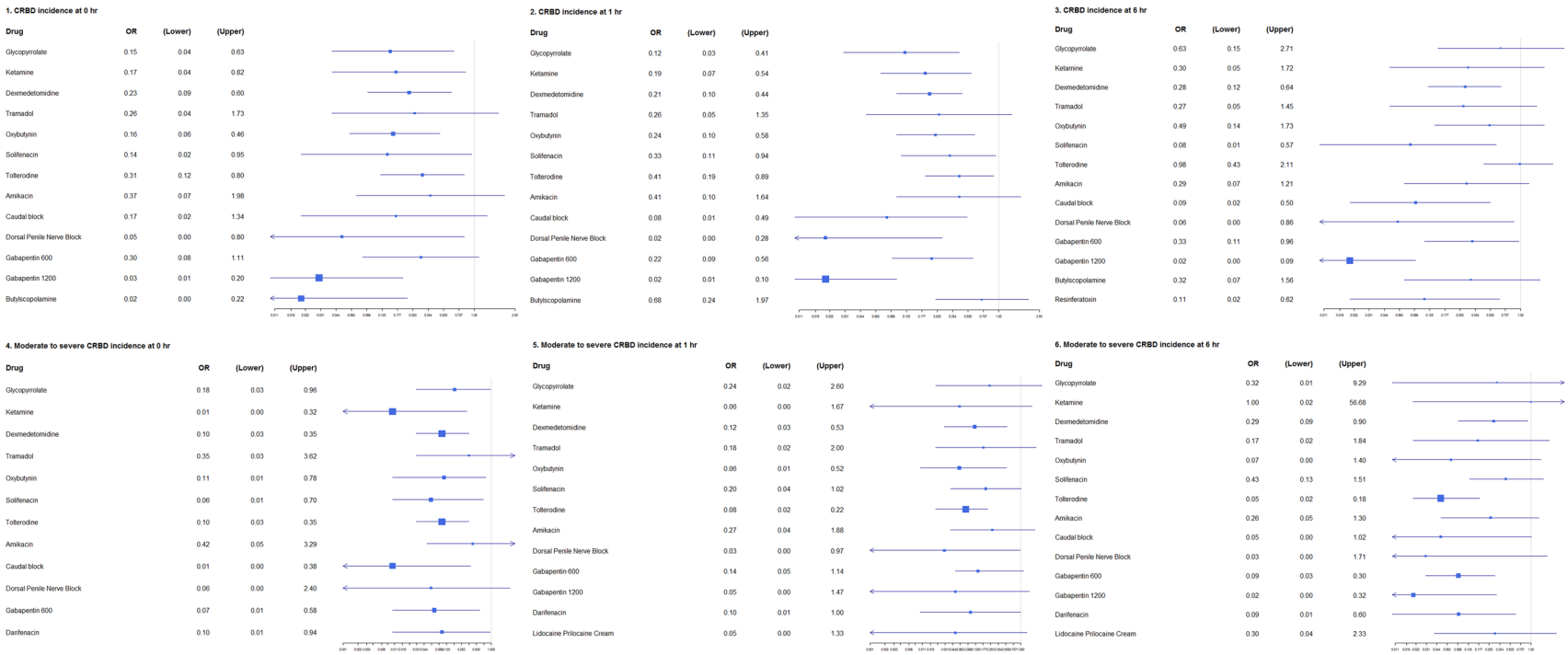

Fig. 2 Forest plots illustrate the network estimates across the included interventions referred to placebo according to 6 different outcomes. *OR* odds ratio. *Gabapentin* 600 gabapentin 600 mg p.o., *Gabapentin* 1200 gabapentin 1200 mg p.o. (Lower) and (upper) means the 95% credible interval

Table 3 Network pooled estimates of the incidence of postoperative catheter-related bladder discomfort at 0 and 1 h after surgery

CRBD at 1 hour after surgery

CRBD at 0 hour after surgery													
Placebo	**0.12 (0.03, 0.41)**	**0.19 (0.07, 0.54)**	**0.21 (0.10, 0.44)**	0.26 (0.05, 1.35)	**0.24 (0.10, 0.58)**	**0.33 (0.11, 0.94)**	**0.41 (0.19, 0.89)**	0.41 (0.10, 1.64)	**0.08 (0.01, 0.49)**	**0.02 (0.00, 0.28)**	**0.22 (0.09, 0.56)**	**0.02 (0.01, 0.10)**	0.68 (0.24, 1.97)
0.15 (0.04, 0.63)	**Glycopyrrolate**	1.64[b] (0.32, 8.34)	1.83 (0.43, 7.84)	2.25 (0.29, 17.7)	2.04 (0.44, 9.51)	2.79 (0.54, 14.4)	3.47 (0.79, 15.3)	3.47 (0.53, 22.7)	0.70 (0.08, 6.27)	0.13 (0.01, 3.15)	1.87 (0.39, 9.03)	0.20 (0.03, 1.32)	5.81 (0.92, 30.2)
0.17 (0.04, 0.82)	1.17[a] (0.14, 9.55)	**Ketamine**	1.11 (0.35, 3.50)	1.37 (0.20, 9.38)	1.24 (0.32, 4.81)	1.70 (0.39, 7.35)	2.11 (0.58, 7.63)	2.11 (0.38, 17.8)	0.43 (0.05, 3.35)	0.08 (0.00, 1.75)	1.14 (0.28, 4.57)	**0.12 (0.02, 0.69)**	3.53 (0.81, 15.4)
0.23 (0.09, 0.60)	1.52 (0.27, 8.55)	1.31 (0.27, 6.34)	**Dexmedetomidine**	1.23 (0.21, 7.36)	1.12 (0.35, 3.53)	1.53 (0.42, 5.52)	1.90 (0.65, 5.53)	1.90 (0.40, 9.12)	0.38 (0.06, 2.66)	0.07 (0.00, 1.45)	1.02 (0.31, 3.38)	**0.11 (0.02, 0.53)**	3.18 (0.88, 11.5)
0.26 (0.04, 1.73)	1.73 (0.16, 18.7)	1.49 (0.13, 17.1)	1.14 (0.14, 9.53)	**Tramadol**	0.91 (0.14, 5.79)	1.24 (0.18, 8.62)	1.54 (0.25, 9.38)	1.54 (0.18, 13.1)	0.31 (0.03, 3.51)	**0.06 (0.01, 0.65)**	0.83 (0.13, 5.45)	**0.09 (0.01, 0.76)**	2.58 (0.37, 18.0)
0.16 (0.06, 0.46)	1.08 (0.18, 6.38)	0.92 (0.14, 5.91)	0.71 (0.17, 2.92)	0.62 (0.07, 5.42)	**Oxybutynin**	1.37 (0.35, 8.31)	1.70 (0.61, 4.75)	1.70 (0.33, 8.81)	0.34 (0.05, 2.53)	0.06 (0.00, 1.35)	0.91 (0.25, 3.31)	**0.10 (0.02, 0.51)**	2.84 (0.71, 11.4)
0.14 (0.02, 0.95)	0.97 (0.09, 10.3)	0.83 (0.07, 9.47)	0.64 (0.08, 5.26)	0.56 (0.04, 8.06)	0.90 (0.10, 7.73)	**Solifenacin**	1.24 (0.34, 4.61)	1.24 (0.27, 7.09)	0.25 (0.03, 2.00)	0.05 (0.00, 1.04)	0.67 (0.16, 2.73)	**0.07 (0.01, 0.41)**	2.08 (0.46, 9.35)
0.31 (0.12, 0.80)	2.06 (0.37, 11.6)	1.76 (0.29, 10.8)	1.35 (0.35, 5.23)	1.19 (0.14, 9.91)	1.91 (0.54, 6.73)	2.12 (0.26, 17.5)	**Tolterodine**	1.00 (0.20, 4.92)	0.20 (0.03, 1.43)	**0.04 (0.00, 0.77)**	0.54 (0.16, 1.83)	**0.06 (0.01, 0.29)**	1.67 (0.45, 6.24)
0.37 (0.07, 1.98)	2.44 (0.27, 22.5)	2.09 (0.21, 20.7)	1.60 (0.23, 11.2)	1.41 (0.11, 17.9)	2.26 (0.31, 16.6)	2.52 (0.20, 31.7)	1.19 (0.17, 8.29)	**Amikacin**	0.20 (0.02, 1.95)	**0.04 (0.00, 0.96)**	0.54 (0.10, 2.89)	**0.06 (0.01, 0.42)**	1.68 (0.29, 9.63)
0.17 (0.02, 1.34)	1.13 (0.09, 14.1)	0.97 (0.07, 12.8)	0.74 (0.08, 7.28)	0.65 (0.04, 10.8)	1.05 (0.10, 10.7)	1.17 (0.07, 19.2)	0.55 (0.06, 5.38)	0.46 (0.03, 6.72)	**Caudal block**	0.19 (0.01, 5.74)	2.67 (0.35, 20.2)	0.29 (0.03, 2.78)	8.29 (0.97, 66.5)
0.05 (0.00, 0.80)	0.33 (0.01, 7.54)	0.28 (0.01, 6.80)	0.22 (0.01, 4.10)	0.19 (0.02, 1.46)	0.30 (0.02, 5.96)	0.34 (0.01, 9.77)	0.16 (0.01, 3.03)	0.13 (0.01, 3.50)	0.29 (0.01, 9.36)	**Dorsal penile nerve block**	14.19 (0.66, 303.0)	1.52 (0.06, 38.5)	44.09 (0.99, 878)
0.30 (0.08, 1.11)	1.99 (0.28, 14.0)	1.70 (0.22, 13.1)	1.31 (0.26, 6.69)	1.15 (0.11, 11.5)	1.84 (0.34, 9.93)	2.05 (0.21, 20.4)	0.97 (0.19, 4.93)	0.81 (0.10, 6.96)	1.76 (0.15, 20.6)	6.07 (0.28, 132.6)	**Gabapentin 600**	**0.11 (0.03, 0.42)**	3.11 (0.75, 12.9)
0.03 (0.01, 0.20)	0.22 (0.02, 2.24)	0.19 (0.02, 2.07)	0.14 (0.02, 1.14)	0.13 (0.01, 1.76)	0.20 (0.02, 1.67)	0.23 (0.02, 3.12)	**0.11 (0.01, 0.84)**	0.09 (0.01, 1.08)	0.20 (0.01, 3.08)	0.67 (0.02, 18.8)	**0.11 (0.02, 0.63)**	**Gabapentin 1200**	**28.94 (4.99, 168)**
0.02 (0.00, 0.22)	0.11 (0.01, 2.16)	0.09 (0.00, 1.95)	0.07 (0.00, 1.16)	0.06 (0.00, 1.59)	0.10 (0.01, 1.69)	0.11 (0.00, 2.82)	0.05 (0.00, 1.01)	0.04 (0.00, 1.01)	0.09 (0.00, 2.71)	0.33 (0.01, 15.2)	0.05 (0.00, 1.03)	0.49 (0.02, 12.0)	**Butylscopolamine**

95% credible intervals are displayed in parenthesis. Row interventions (denominator) was compared to column intervention (numerator) for the incidence of CRBD at 0 h and column intervention (numerator) was compared to row interventions (denominator) for the incidence of CRBD at 1 h after surgery

For example, [a]ketamine vs. glycopyrrolate for the incidence of CRBD at 0 h

[b]Ketamine vs. glycopyrrolate for the incidence of CRBD at 1 h after surgery

Bold numbers mean statistical significance

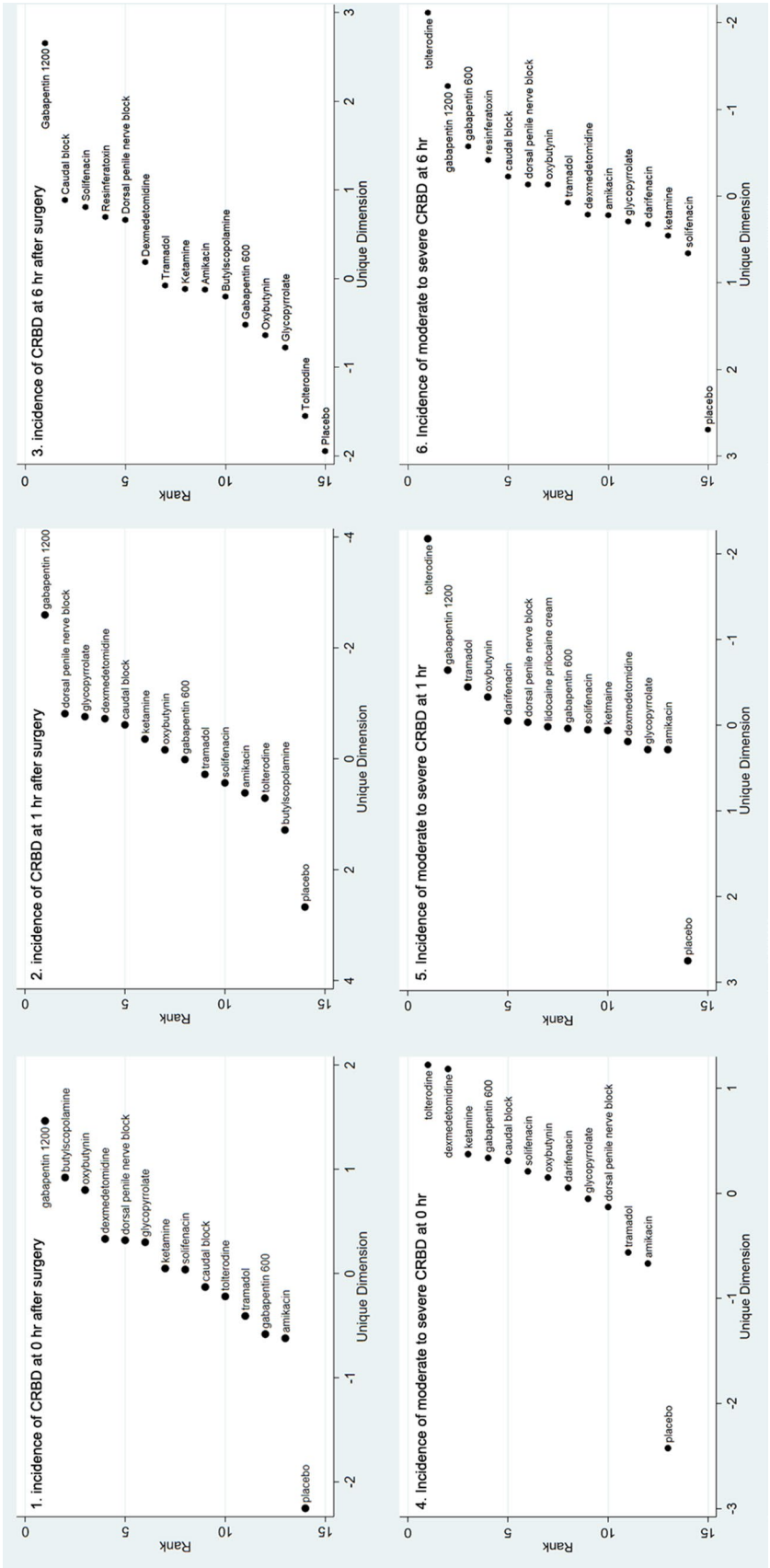

Fig. 3 Relative ranking plots of interventions based on multidimensional scaling approach. The upper located interventions are ranked higher than the intervention located lower

between included studies. Table 4 shows the GRADE quality of evidence for the CRBD at 1 h and Supplemental Table S7 shows the GRADE quality of evidence for all other outcomes. All comparisons were at moderate to low quality of evidence and many comparisons were downgraded due to imprecision due to the 95% CI was wide or crossed unity.

Discussion

We performed a systematic review and network meta-analysis comparing 15 interventions for preventing CRBD after surgery. Although our network meta-analysis was limited by a small number of studies and heterogeneity of enrolled studies, we obtained comparative effectiveness of these interventions regarding incidence and severity of CRBD that developed after surgery. The major findings of our study were as follows: (1) gabapentin 1200 mg p.o. was ranked best regarding incidence of CRBD at 0, 1, and 6 h after surgery, (2) tolterodine was ranked best regarding the severity of CRBD at 0, 1, and 6 h after surgery, and (3) significant heterogeneity exists among the included RCTs regarding patient demographics and type of surgery. Despite paucity and poor quality of evidence, we report our network meta-analysis because there have been no head-to-head comparisons of many investigated drugs for managing CRBD after urologic surgery.

CRBD, defined as an urge to void or suprapubic discomfort, is common in the patients who have an indwelling urinary catheter in the postoperative period. According to previous studies, the incidence of CRBD is 55–91% after surgery [1, 22, 32]. CRBD can be expressed after all surgeries requiring urinary catheterization during the perioperative period, but is more common in urologic surgery, especially after transurethral resection of bladder tumors.

CRBD shows symptoms similar to overactive bladder (OAB) that is characterized by the urinary frequency, urgency, with or without urge incontinence that negatively influenced the patients' quality of life. These symptoms of the two disease entities were thought to be due to involuntary bladder contraction due to muscarinic receptor stimulation and bladder spasm due to local irritation. Since CRBD and OAB have been shown to share similar symptoms and mechanisms, a number of studies have been conducted to evaluate

Table 4 The grade of recommendation, assessment, development, and evaluation (GRADE) approach summary of findings table with the quality of evidence for all comparisons of the incidence of catheter-related bladder discomfort at 1 h after surgery

Comparison	Direct evidence		Indirect evidence		Network meta-analysis	
	OR (95% CI)	GRADE	OR (95% CrI)	GRADE	OR (95% CI)	GRADE
Glycopyrrolate vs. placebo	**0.12 (0.05, 0.31)**	⊕⊕⊕O Moderate[c]	**0.12 (0.01, 0.98)**	⊕⊕OO Low[c,d]	**0.12 (0.03, 0.41)**	⊕⊕⊕O Moderate[c]
Ketamine vs. placebo	**0.20 (0.10, 0.40)**	⊕⊕⊕O Moderate[c]	0.19 (0.03, 1.30)	⊕OOO Very low[a,b,c]	**0.19 (0.07, 0.54)**	⊕⊕⊕O Moderate[c]
Dexmedetomidine vs. placebo	**0.20 (0.12, 0.31)**	⊕⊕⊕O Moderate[c]	0.21 (0.04, 1.15)	⊕OOO Very low[a,b,c]	**0.21 (0.10, 0.44)**	⊕⊕⊕O Moderate[c]
Tramadol vs. placebo	**0.26 (0.08, 0.85)**	⊕⊕⊕O Moderate[d]	0.26 (0.02, 3.16)	⊕⊕OO Low[a,b]	0.26 (0.05, 1.35)	⊕⊕OO Low[a,b]
Oxybutynin vs. placebo	**0.21 (0.08, 0.55)**	⊕⊕⊕O Moderate[c]	0.24 (0.04, 1.44)	⊕OOO Very low[a,b,c]	**0.24 (0.10, 0.58)**	⊕⊕⊕O Moderate[c]
Solifenacin vs. placebo	0.29 (0.05, 1.82)	⊕⊕OO Low[a,c]	0.33 (0.05, 2.26)	⊕OOO Very low[a,b,c]	**0.33 (0.11, 0.94)**	⊕⊕OO Low[c,d]
Tolterodine vs. placebo	**0.44 (0.29, 0.68)**	⊕⊕⊕O Moderate[c]	0.41 (0.07, 2.27)	⊕OOO Very low[a,b,c]	**0.41 (0.19, 0.89)**	⊕⊕OO Low[c,d]
Amikacin vs. placebo	**0.41 (0.18, 0.91)**	⊕⊕OO Low[c,d]	0.41 (0.04, 3.82)	⊕OOO Very low[a,b,c]	0.41 (0.10, 1.64)	⊕⊕OO Low[a,c]
Caudal block vs. placebo	**0.08 (0.02, 0.33)**	⊕⊕⊕O Moderate[c]	0.08 (0.01, 1.16)	⊕OOO Very low[a,b,c]	**0.08 (0.01, 0.49)**	⊕⊕⊕O Moderate[c]
DPNB vs. placebo	**0.06 (0.01, 0.49)**	⊕⊕⊕O Moderate[c]	**0.02 (0.00, 0.77)**	⊕⊕⊕O Moderate[c]	**0.02 (0.00, 0.28)**	⊕⊕⊕O Moderate[c]
Gabapentin 600 vs. placebo	**0.21 (0.06, 0.75)**	⊕⊕OO Low[c,d]	0.22 (0.03, 1.38)	⊕OOO Very low[a,b,c]	**0.22 (0.09, 0.56)**	⊕⊕⊕O Moderate[c]
Gabapentin 1200 vs. placebo	**0.03 (0.01, 0.10)**	⊕⊕⊕O Moderate[c]	**0.02 (0.00, 0.22)**	⊕⊕⊕O Moderate[c]	**0.02 (0.01, 0.10)**	⊕⊕⊕O Moderate[c]
Butylscopolamine vs. placebo	0.73 (0.12, 4.34)	⊕⊕OO Low[a,c]	0.68 (0.10, 4.74)	⊕⊕OO Low[a,c]	0.68 (0.24, 1.97)	⊕OOO Very low[a,b,c]

CI confidence interval, *CrI* credible interval

[a]Very serious imprecision since 95% confidence interval crosses unity and with wide confidence interval suggesting high probability of harm

[b]Inconsistency

[c]Unclear or high risk of bias

[d]serious imprecision with wide confidence or predictive interval

whether effective agents in OAB including anticholinergics are also effective in CRBD. The symptoms of CRBD are known to be related to types 2 and 3 (M2 and M3 receptors) among the five types of muscarinic receptors [33]. The M3 receptor is responsible for 'direct contraction', whereas the M2 receptor is related to 'indirect re-contraction' by reversing the relaxation induced by a cyclic adenosine monophosphate (cAMP)-induced beta-adrenergic effect [33].

Gabapentin that was the most effective for reducing the overall incidence of CRBD is a structural analog of the inhibitory neurotransmitter gamma-aminobutyric acid. Gabapentin is an antiepileptic and anti-nociceptive drug. Gabapentin is thought to act by binding to the α2δ subunit of voltage-activated calcium channels, but the exact mechanism of its action is not yet clear. Gabapentin inhibits peripheral sensitization by inhibitory activity on afferent C-fibers and also has central action within the spinal cord or brain reducing the sensitization of dorsal horn neurons [8]. This combined action of gabapentin on the peripheral and central nervous system might have contributed to reducing the incidence of CRBD.

Intriguingly, gabapentin 1200 mg p.o. was superior in reducing the overall incidence of CRBD, but not in reducing the incidence of moderate to severe CRBD, although gabapentin 1200 mg p.o. was also ranked second in reducing severity. This may be because there were very small data reporting the severity of CRBD after gabapentin compared to the incidence of CRBD. There was only one study that reported the severity of CRBD after administration of gabapentin [22], while there were three studies that reported the severity of CRBD after tolterodine [1, 2, 32].

According to our results of network analysis, tolterodine was suggested to be the most effective in reducing the severity of CRBD. Tolterodine is a kind of antimuscarinic agent that was developed to treat overactive bladder. Tolterodine has demonstrated a bladder-selective profile in vivo and acts on both M2 and M3 subtypes of muscarinic receptors [34, 35]. A mixed population of M2 and M3 muscarinic receptors exists in the smooth muscle of the human urinary bladder. Although the M2 receptors are the predominant receptor of the bladder (70–80%), M3 receptors seem to be functionally important and are responsible for detrusor contraction [34]. Solifenacin and darifenacin are the selective M3 and M2 receptor blocker with a greater selectivity of M2 and M3 receptor subtype compared to old antimuscarinic agents [36]. Therefore, receptor affinity could not explain our result of the superiority of tolterodine in reducing the severity of CRBD.

There was only a few previous literature reviewing the drugs or interventions for CRBD. Hu et al. [13] conducted a classic meta-analysis pooling eight studies of tramadol, gabapentin, ketamine, oxybutynin, and other anticholinergic drugs including butylscopolamine and tolterodine. They found that ketamine, anticholinergic drugs, tramadol, and gabapentin significantly decreased the incidence and severity of postoperative CRBD. Bai et al. [12] performed a narrative review including 14 studies published between 2005 and 2014. They reported that muscarinic antagonist, anesthetics, antiepileptics, and analgesics all significantly reduced the symptom and incidence of CRBD compared to placebo. They suggested that surgery that is the most refractory to treatment may be transurethral resection of bladder tumor.

The transitivity and consistency assumption should be considered to perform a network meta-analysis. The studies enrolled should be sufficiently similar enough to be integrated. Our included studies consist of heterogeneous patient groups with a different distribution of age, gender, and type and duration of surgery. The Foley catheter size varied across the studies. In an observational study, the diameter of the Foley catheter greater than 18 Fr and male gender were associated with moderate or severe CRBD in the PACU [37]. The consistency of plot of our primary outcome demonstrated that ROR ranged from 1.019 to 2.932 with a wide confidence interval, although the τ^2 were small. This may be due to a wide confidence interval of network estimate calculated from small sample size. Given the transitivity and consistency assumption, a firm conclusion cannot be drawn from our network analysis.

Our study has several important limitations. First, as mentioned above, significant heterogeneity exists across the study. Our results should be interpreted under this limitation. Second, most of the studies were small RCTs and more than half of them were at unclear or high risk of bias. The number of study for each intervention was small. Subgroup analysis or sensitivity analysis could not be conducted due to the small number of studies. Our network meta-analysis results should be interpreted cautiously considering the paucity and poor quality of evidence. Paucity and poor quality of evidence decrease the quality of network estimate by increasing the proportion of indirect evidence and loop-specific heterogeneity [15, 38, 39]. Third, each drug or intervention has its own complications including anticholinergic effect, sedation, nausea and vomiting, and respiratory depression. As these side effects could not be compared in our network, drug complications should be considered according to each patient. Fourth, the judgement of the level of CRBD may be influenced by the sedative effects of dexmedetomidine and gabapentin. The sedative effects may be considered when we interpret our results.

In conclusion, our first network meta-analysis of the interventions preventing CRBD after surgery demonstrated that gabapentin 1200 mg p.o. was ranked best in decreasing the overall incidence of CRBD and tolterodine was ranked best in decreasing the severity of CRBD during the 6 h after surgery. However, our results were limited by the small number of study for each intervention and the heterogeneous patients

with a different distribution of age, gender, and type of surgery. Whether this statistical inference translates into clinically relevant differences still remains to be determined in the future studies with a head-to-head comparison of these interventions. More reliable network estimates will be calculated with further high-quality studies of head-to-head comparisons.

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Compliance with ethical standards

Conflict of interest The authors declared that they have no conflicts of interests.

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