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REVIEW

Combination of solifenacin and tamsulosin may provide additional beneficial effects for ureteral stent-related symptoms—outcomes from a network meta-analysis

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Abstract

Purpose To systematically evaluate the different efficacy among generally used drugs for stent-related symptoms (SRS) with the method of network meta-analysis.

Methods A systematic search was performed in the US National Library of Medicine's life science database (Medline), Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database for Systematic Reviews before December 2017. Analysis was performed under multivariate random-effects network model and effects of drugs were ranked with surface under the cumulative ranking (SUCRA) probabilities.

Results 19 trials with 2036 patients investigating 4 different intervention including tamsulosin (Tam), alfuzosin (Alfu), solifenacin (Soli) and combination of Tam and Solif were finally included in our analysis. Tam plus Soli had the highest SUCRA on all aspects of ureteral stent symptom questionnaire: urinary symptoms (86.2%), body pain (85.0%), general health (80.5%), work performance (72.0%) and sexual performance (84.4%). Except for pain relief, Soli showed higher SUCRA than Tam or Alfu in rest respects. Tam and Alfu showed similar SUCRA on urinary symptoms (53.0 vs 48.7%) and body pain relief (61.9 vs 62.9%).

Conclusions Tam plus Soli might be the most effective intervention for SRSs. As for monotherapy, Soli showed advantages in most respects except for pain relief compared to Tam or Alfu. Tam and Alfu showed similar efficacy on urinary symptoms and body pain relief.

Keywords Ureteral stent-related symptoms · Network meta-analysis · Drug therapies

Introduction

Internal ureteral stents has become one of the most common urologic procedures since first introduced in 1967 [1]. However, stent-related symptoms (SRSs) such as lower urinary tract symptoms (LUTS) [2] and pain [3] with declines of quality of life (QoL) are recorded in majority of patients. Great efforts on physical properties of stent have been made to reduce the incidence of SRS including the material, stent design, length, position and coatings. Meanwhile, different oral medications such as α-blockers, anticholinergic agents, analgesics and anti-inflammatory drugs or their combinations are reported for reducing SRSs [4].

Nevertheless, there are controversial evidences on if the combination of drugs can provide preferable effect. Though a meta-analysis reported that combination of solifenacin and tamsulosin did not show beneficial effects over solifenacin monotherapy, the network meta-analysis [5] is a newly introduced method in which multiple treatments can be directly or indirectly compared even if they are not designed in a same RCT but with same control group [6] and can show us the most probable best treatment. In addition, it is difficult for traditional meta-analysis to explain such topic comprehensively because it can only synthesis evidence from the

Zhongyu Jian and Yuntian Chen contributed equally to this work.

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head-to-head trial. Network meta-analysis is an effective solution to such problems. It can make indirect comparison using a common comparator when a head-to-head trial is not available. It also can combine direct and indirect comparisons to simultaneously compare several treatments with preservation of randomisation in individual trials.

There is no network meta-analysis that compares the different α-blockers or anticholinergic agents based on Ureteral Stent Symptoms Questionnaire (USSQ) until now. The current study tended to examine available RCTs to explore the effects of α-blockers, anticholinergics and their combination on stent-related symptoms based on USSQ. We plan to find which treatment maybe the best intervention according to the network meta-analysis method.

Materials and methods

We performed systematic reviews according to the latest Preferred Reporting Items for Systematic reviews and Meta-analyses Statement (PRISMA) [7].

Search strategy and selection criteria

We searched the US National Library of Medicine's life science database (Medline), Embase, the Cochrane Central Register of Controlled Trials, and the Cochrane Database for Systematic Reviews before December 2017. The language of publication was limited on English and full-text availability. We imposed no restrictions on year of publication. Keywords involved "alpha blocker (s)," "tamsulosin," "alfuzosin," "antimuscarinic (s)," "solifenacin," "tolterodine," "stent(s)," "ureteral," and their all multiple synonyms.

Studies that met all of the following were included: (1) randomized controlled trails on the drug treatments for ureteral stent-related symptoms (SRS). (2) Ureteral stent symptom questionnaire (USSQ) was used to assess the outcome. (3) Regimens to be included should have been investigated with at least one scale in at least in two studies to get pooled outcome. (4) Crossover trials, dose titration studies, daily dosing studies and studies that were only available as abstracts were excluded. (5) Studies adopting International Prostate Symptom Score (IPSS) or visual analogue pain scale (VAPS) or the quality of life (QoL) or self-made questionnaires were excluded.

Outcome measures and data extraction

The data were extracted by two independent reviewers. A third reviewer resolved any disagreements. Summary estimates per group (mean, changes in means) with measures of variability [standard deviation (SD), 95% confidence interval (CI)] as available were extracted for continuous data. The primary outcomes measurements were total score for two index namely urinary symptoms and body pain of the USSQ. Other outcomes measurements were the rest index of USSQ including general health, work performance, sexual performance and additional problems and drug-related side effects. When a standard deviation (SD) was not provided, it was calculated with the P value or imputed from other trials included the meta-analysis using the formula:$\mathrm{SD}_{\mathrm{pooled}} = \sqrt{\frac{\sum(n_i-1)\mathrm{SD}_i^2}{\sum(n_i-1)}}$ [8].

Quality assessment

The quality assessments of eligible studies were evaluated using the Cochrane Risk of Bias tool. The items included randomization, blinding, dropout, eligibility criteria for participants, adverse events, and statistical methods. The judgments for each entry involved were divided into three grades: "high", "unclear", and "low". A quality assessment was performed by two independent reviewers, and disagreements were resolved by consensus.

Statistical analysis

The meta-analysis outcomes were divided into five groups based on USSQ: urinary symptoms, body pain, general health, work performance and sexual performance.

Outcomes were gauged by a standard multivariate random-effects network model [30]; the mean differences (MD) with 95% CIs (confidence interval) of each intervention compared with control or any two interventions compared with each other were worked out. If the 95% CI was above or under 1.00, then the difference was statistically significant ($P < 0.05$).

We used the surface under the cumulative ranking curves (SUCRA) probabilities to assess the efficacy of different drugs, which was a common and popular method used in network-meta analysis [9]. SUCRA expresses a percentage of the efficacy of every intervention compared to an imaginary intervention that is always the best without uncertainty. A SUCRA value of 100% is assigned to the best treatment and 0% for the worst treatment.

Network of the included comparisons was shown through network graph. Nodes are proportional to the number of patients included in the included treatments, and edges are weighed according to the number of studies included in the comparisons. A comparison-adjusted funnel plot was used to assess the presence of small-study effect and publication bias. Inconsistency was tested by Higgins and Dias model and $P < 0.05$ indicated inconsistency existed in network meta-analysis.

All the analyses were performed with Stata 14 (Stata Corp, College Station, TX, USA).

Results

The flowchart of study identification and inclusion process is seen in Fig. 1. Finally, there were 19 trials with 2036 patients investigating 4 different intervention as follows: subtype selective α1-blockers group (tamsulosin) which has high affinity for α1a-adrenergic receptors (α1aAR) and α1d-adrenergic receptors (α1dAR) subtypes but not for α1b-adrenergic receptors (α1bAR), non-subtype selective α1-blockers group (alfuzosin), anticholinergic agent group (solifenacin) and combination group (tamsulosin + solifenacin), that met our including criteria [10–28]. However, 16 trials with 1639 patients were further pooled into network meta-analysis because that data of other three studies [22, 23, 25] could not be extracted. For urinary symptoms efficacy assessment, 16 trials [10–21, 24, 26–28] were included in our network meta-analysis. And for pain-relief efficacy there were 15 trials [10–14, 16–21, 24, 26–28] enrolling into further network meta-analysis. For general health, work performance and sexual performance, total of 12 trials [10, 12–14, 17–21, 24, 27, 28] were included in our further analysis. What need to be announced was that most of studies testing tolterodine, doxazosin and terazosin were excluded from our meta-analysis because they used the IPSS questionnaire.

Five individual network-meta analyses were done to compare the efficacy of different drugs based on USSQ-symptom scales including 5 nodes. The median follow-up period range from 1 to 6 weeks. The detailed information for each article is shown in Supplementary Table 1. An assessment of each randomized control trial based on Cochrane library guideline was conducted. The detail of assessment is shown in Supplementary Figure 1.

SUCRA and inconsistency test are summarized in Table 1, details were described as follows.

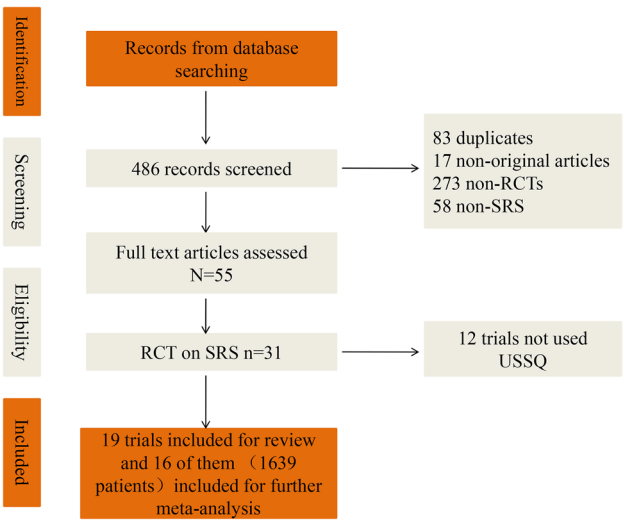

Fig. 1 Preferred reporting for systematic reviews and meta-analyses flow diagram. *SRS* stenting related symptom. *RCT* randomized controlled trial. *USSQ* Ureteral Stent Symptoms Questionnaire

The urinary symptoms relief efficacy analysis

The results of the network meta-analysis are shown in Fig. 2. Analysis included tamsulosin (Tam), solifenacin (Soli), tamsulosin + solifenacin (Tam + Soli) and alfuzosin (Alfu), network graph is seen in Fig. 2a. When placebo was used as the reference for the comparison, the Tam [MD, − 5.10; 95% CI (− 7.55, − 2.64)], Alfu [MD, − 4.31; 95% CI (− 7.11, − 0.91)], Soli [MD, − 5.79; 95% CI (− 8.38, − 3.20)] and Tam + Soli [MD, − 8.02; 95% CI (− 11.97, − 4.07)] treatments were associated with a statistically significant increase in the urinary symptoms. There was no significant difference in the urinary symptoms among these regimens (Fig. 2b). The summary league table of comparisons is shown in Fig. 2c. The SUCRA values provided the hierarchy for the five treatments. The network analysis suggested that the Tam + Soli had the highest probability to be the best intervention for urinary symptom relieving (SUCRA 86.2%, mean rank 1.5), followed by the Soli (SUCRA 61.6%, mean rank 2.5) and Tam (SUCRA 53.0%, mean rank 2.9). The Alfu might be the worst one among the four interventions (SUCRA 48.7%, mean rank 3.1) (Fig. 2c).

Table 1 The summary of SUCRA and Inconsistency test

Outcomes	SUCRA					Inconsistency test	
	Tam + Soli (%)	Soli (%)	Tam (%)	Alfu (%)	Control (%)	Chi^2	Pro > Chi^2
Urinary symptoms	86.2	61.6	53	48.7	0.5	6.53	0.3662
Body pain	85	62.9	61.9	39.6	0.6	5.55	0.4755
General health	80.2	75.7	50.4	39.5	3.8	1.07	0.9830
Work performance	72	64.6	44.8	37	31.7	1.62	0.9508
Sexual performance	84.4	67.7	54.4	26.5	16.8	1.06	0.9834

SUCRA surface under the cumulative ranking curves, *Tam* Tamsulosin, *Alfu* Alfuzosin, *Soli* Solifenacin

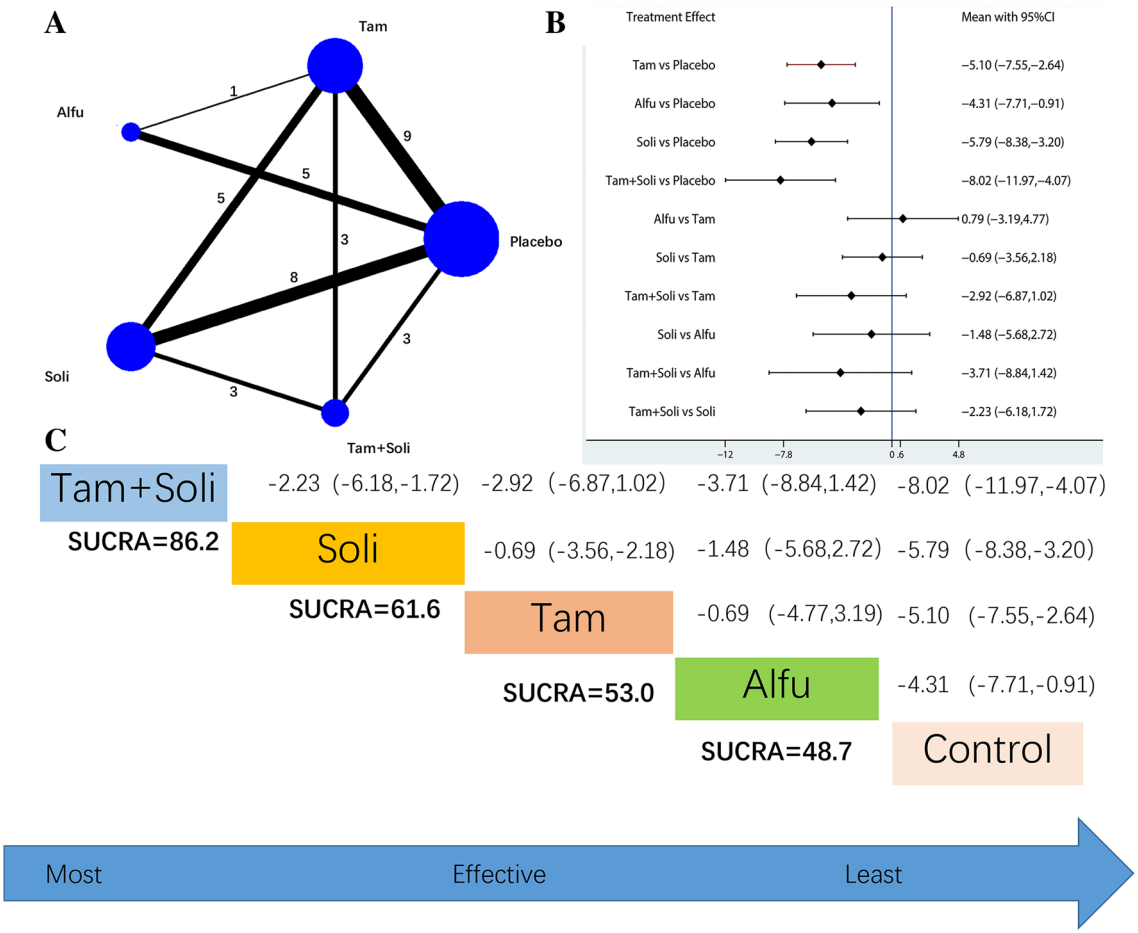

Fig. 2 Network analysis of symptom-relieve efficacy of different interventions. **a** Network graph of comparison included in the analysis. **b** Forest plot of network-meta analysis. **c** The summary league table of comparisons and SUCRA rank

The pain-relief efficacy analysis

The results of the network meta-analysis are shown in Fig. 3. Analysis included Tam, Soli, Tam + Soli and Alfu, network graph is seen in Fig. 3a. Compared to the placebo, Tam [MD, − 4.57; 95% CI (− 6.72, − 2.41)], Soli [MD, − 3.23; 95% CI (− 5.43, − 1.03)], Tam + Soli [MD, − 6.86; 95% CI (− 10.38, − 3.34)] and Alfu [MD, − 4.35; 95% CI (− 8.07, − 0.64)] showed significant advantages in pain relief. There was a significant difference between Tam + Soli and Soli [MD, − 3.63; 95% CI (− 7.24, − 0.03)] (Fig. 3b). These data suggest that the combination regimen was generally better than the monotherapy regimen in terms of the body pain. The summary league table of comparisons is shown in Fig. 3c. The SUCRA point also suggested the Tam + Soli to have the highest probability to be the best choice for pain-relief on SRS patients (SUCRA 85.0%, mean rank 1.6), followed by the Alfu (SUCRA 62.9%, mean rank 2.5) and Tam (SUCRA 61.9%, mean rank 2.5). The Soli, according to the SUCRA point (SUCRA 39.6%, mean rank 3.4), might be the worst one among the four interventions (Fig. 3c).

The general health, working performance and sexual matters analysis

Only Tam + Soli (MD, − 2.27; 95% CI (− 4.18, − 0.36)] and Soli [MD, − 2.01; 95% CI (− 3.41, − 0.62)] regimens showed significant advantage when compared with the placebo which suggested that the combination regimen and Soli might be better than the other two regimens in terms of general health. Not surprisingly, the network-analysis suggested that Tam + Soli and Soli might be the top two choices for the general health scale (SUCRA 80.5% and SUCRA 75.7%, respectively), followed by Alfu (SUCRA 50.4%) and Tam (SUCRA 39.5%) (Supplementary Figure 2).

No significant difference was shown among these treatments in working performance scale. However, The SUCRA values provided the hierarchy for the four active regimens

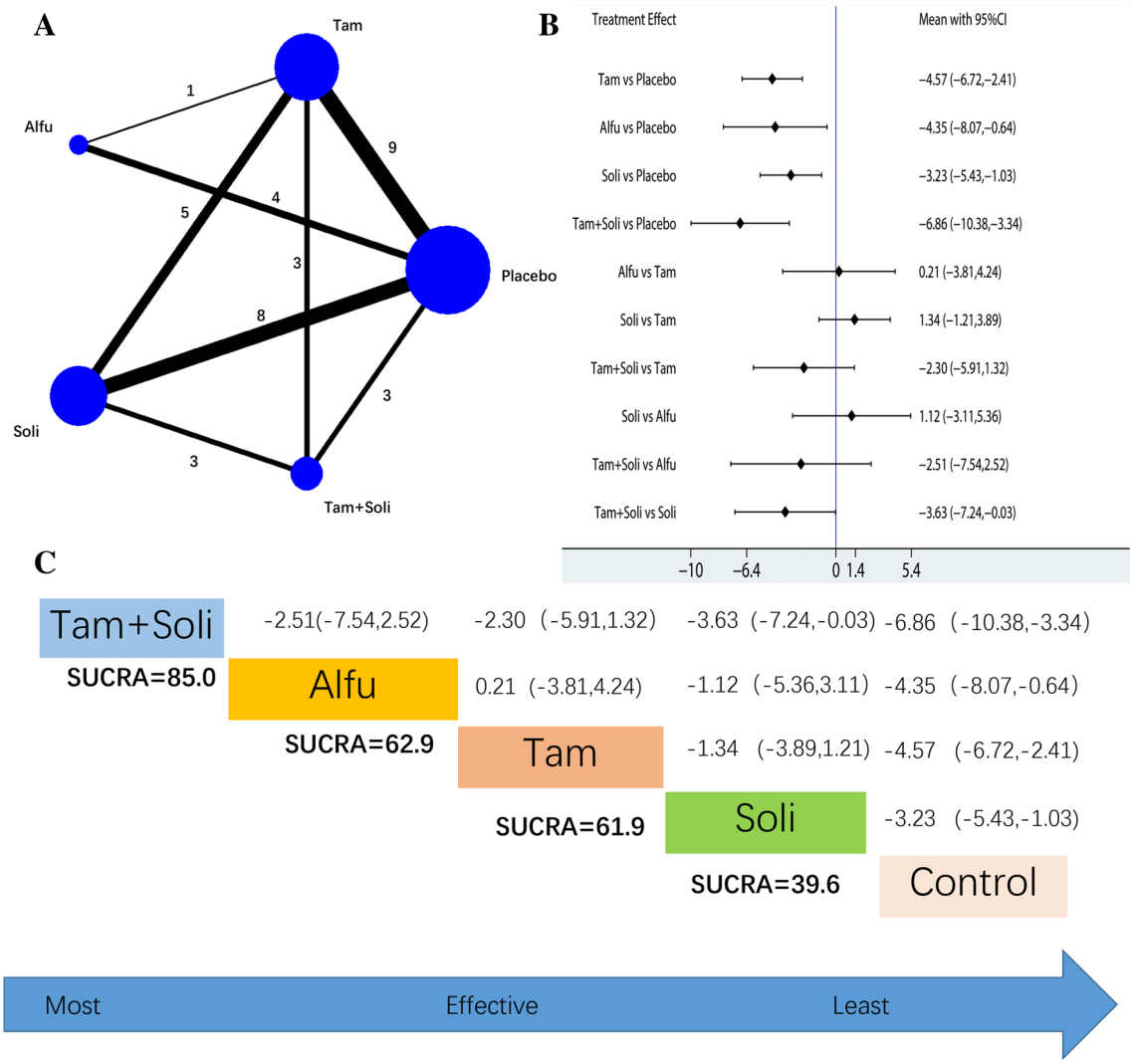

Fig. 3 Network analysis of pain-relieve efficacy of different interventions. **a** Network graph of comparison included in the analysis. **b** Forest plot of network-meta analysis. **c** The summary league table of comparisons and SUCRA rank

and were 72.0, 64.6, 44.8, and 37.0%, for Tam + Soli, Soli, Tam, and Alfu, respectively (Supplementary Figure 3).

Similar to the working performance, there was no significant difference among these treatments. SUCRA rank suggested that Tam + Soli had the highest probability to be the best intervention for sexual matters improvement for SRS patients (SUCRA 84.4%), while the Alfu might be the worst one for sexual matters improvement (SUCRA 26.5%). Soli (SUCRA 67.7%) and Tam (SUCRA 54.5%) took the mid position (Supplementary Figure 4).

Additional problems and drug treatment-related side effects

We did not pool the additional problems score into the meta-analysis because of the limited data. Seven studies of which three studies [10, 11, 17] used dichotomous variables and four studies [12, 14, 20, 28] used continuous variables evaluated the additional problems. Two studies [10, 12] comparing alfuzosin and control group showed similar results. Two [14, 20] of three studies reported that tamsulosin showed a significant advantage compared to control group and the remaining one [11] found that there was no significant difference between two groups. The comparison between solifenacin and control was not the same. Abdelaal [20] reported that solifenacin was better than control group while there was no significant difference in Ragab [28] study between two groups. As for tamsulosin and solifenacin combination, only one study [20] reported additional problems and showed a significant benefit compared to control group.

Though no serious adverse event was reported among the studies, common drug treatment-related side effects

were reported in a few studies such as dry mouth [13, 16, 22, 23, 26, 28], constipation [13, 16, 18, 22, 26], dizziness [13, 15, 18, 23] and headache [13, 16, 18, 22, 26, 28]. Same as the additional problems, we did not pool the side effects into network meta-analysis because of limited data. According to these studies, drug-related side effects did occur because of the use of alpha-blockers and antimuscarinics. But they were tolerant and few participants withdrew the trials because of these side effects.

Risk of bias

The inconsistency results of five network meta-analysis by Higgins model are shown in Table 1. All *P* value was more than 0.05 which indicated that no evidence showed inconsistency existing in the network model. The inconsistency tests were the same in Dias model. The difference between direct comparison and indirect comparison is not statistically significant ($P > 0.05$) (Supplementary Figure 5). All the above tests showed that the network meta-analysis model was good fit for assessment in all five contents of USSQ. Besides, Fig. 4 shows a comparison-adjusted funnel plot of the studies included in this meta-analysis that reported body pain. Most of the studies were evenly distributed inside the 95% CIs, and an almost horizontal line meant a low risk of small sample effect. The funnel plots of the studies reported other terms that showed similar results such as body pain.

Discussion

So far there was no ideal stent that can avoid SRS and with the limited possibilities to prevent SRSs, their medical treatment became even more important. Among many questionnaires, USSQ consisting of six component index of urinary symptoms, body pain, general health, work performance, sexual matters, and additional problems assessed the whole spectrum of stent-associated morbidity, and facilitated better comparability of the data in the SRS field compared to the International Prostate Symptom Score (IPSS), Quality of Life (QoL), Visual Analogue Pain Scales (VAPS), and Overactive Bladder (OAB) questionnaires [29]. Therefore, only studies using USSQ were included in our analysis.

In a direct pair-wise meta-analysis of publications that compared the Soli, as monotherapy or combination reported that Soli had an efficacy in reducing SRSs, but no significant advantage was found over Tam. In addition, combination of Soli and Tam did not show beneficial effects over solifenacin monotherapy [5]. On the basis of the results of the indirect network meta-analysis that compared the various regimens, all regimens (including the Tam, Alfu, Soli, and Tam + Soli) were significantly better than placebo in urinary symptoms and body pain relief. In particular, of all the regimens, Tam + Soli was the most effective treatment for achieving SRS relief on the basis of the summary league table and the SUCRA values.

The strengths of the present study are as follows. To our knowledge, our study was the first network meta-analysis

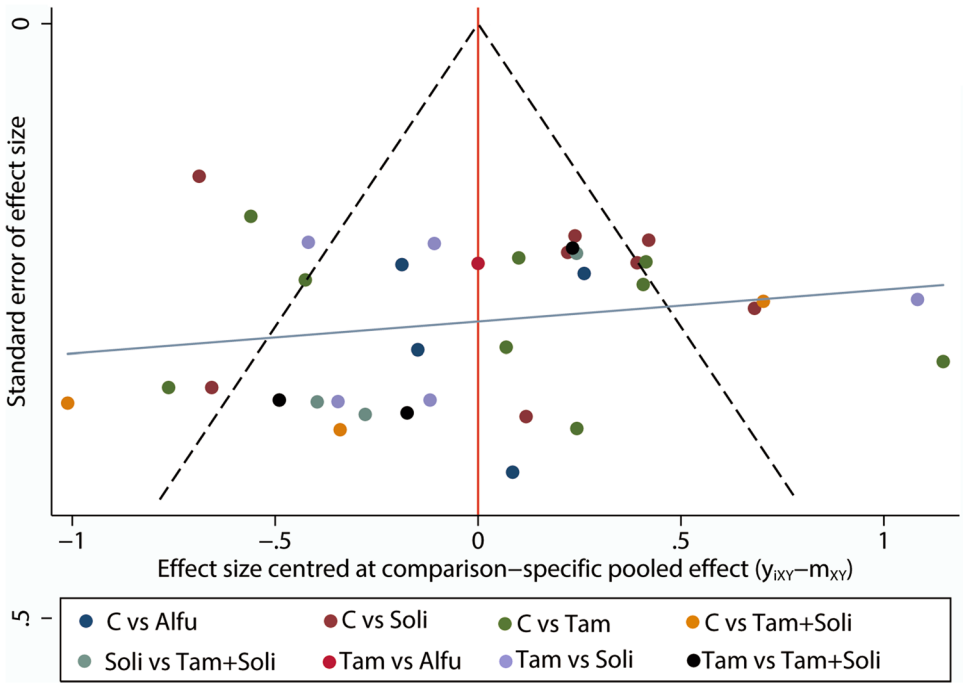

Fig. 4 Comparison-adjusted funnel plot of the studies included in this meta-analysis. *Tam* Tamsulosin, *Alfu* Alfuzosin, *Soli* Solifenacin, *C* control

that reviewed the efficacy and safety of oral medication treatment for SRSs based on all RCTs using USSQ which might provide basic evidence to select an appropriate treatment for ureteral stenting patients. In addition, to compare the different regimens, we conducted a network meta-analysis based on a multivariate random-effects network model [30], and therefore, we could obtain the information with reference to a hierarchy and the relative variance of the effects of each regimen. For any meta-analysis, there are three core assumptions that should be considered namely homogeneity, consistency and similarity. In our study, the approach of using a random effect model gave more conservative results. The inconsistency and publication bias were not significant in our meta-analysis. Similarity was assessed by a detailed examination of the trial characteristics. In our study, all the included studies were RCTs and all the outcomes were measured by USSQ questionnaires. Besides, the quality of each study was conducted based on Cochrane library guideline and showed relative high quality scores.

Some findings were discussed based on SUCRA results as follows. Tam was the most investigated drug in the current study and proven to be effective in reducing SRS. As a drug of similar pharmacologic function, Alfu also showed relieving effect on SRSs but seemed inferior to Tam in sexual performance and work performance respects. In addition, Alfu showed a similar result compared to Tam in urinary symptoms. However, Alfu seemed to be more effective than Tam on general health respect and showed a very puny advantage on body pain relief. Soli was better than Tam and Alfu in relieving urinary symptoms, general health, work performance and sexual performance. On the contrary, Soli was less effective than Tam and Alfu in body pain relief. Further improvements for SRSs were observed when Tam was given with the combination of Soli in all respects including urinary symptom, body pain, general health, work performance and sexual performance.

Outcomes of the current network meta-analysis indicated that with different pharmacological mechanisms, a combination of α-blockers Tam and antimuscarinic agents Soli might have a synergistic effect on SRSs, owing to the simultaneous inhibition of receptors on smooth muscle located in bladder neck region, lower segment of ureter and detrusor. Concerning monotherapy, we found that α-blockers and antimuscarinic agents provided different efficacy on different contents of USSQ. Except for pain relief, Soli showed better results on urinary symptoms, general health, work performance and sexual performance. Stent-induced LUTS was considered to be associated with mechanical irritation of stents on bladder. So with the inhibitive effect on M-receptors of detrusor smooth muscle cell, Soli may be able to handle these symptoms more effectively. Alpha-blockers had been proved able to inhibit ureteral contractility and decreased peak ureteral contraction pressures, which may prevent continuously contracted state of the ureteral smooth muscle caused by the indwelling stent [31], resulting in ureter dilation and improvement in drainage. Therefore, alpha-blockers, by reducing muscle spasm and vesicoureteric reflux, can effectively release body pain. However, compared to control group Soli still showed an obvious advantage on pain relief. Anticholinergic medications had the ability to inhibit abnormal activity of bladder smooth muscle and decreased local contractions of the detrusor [32]. We inferred this might reduce the frequency of rise in intrapelvic pressure induced by bladder contraction and urine reflux, bringing in less onset of pain. As for the comparison between Tam and Alfu, two alpha-blockers were shown to be almost equally effective on urinary symptoms and body pain index scores. Alfu was inferior to Tam in other domains involved, namely sexual performance and work performance.

Admittedly some limitations should be acknowledged. First, follow up of most studies included in our network meta-analysis ranged from 1 to 2 weeks. There was little study reporting how SRSs change over time. Liu [23] found that symptomatic scores decreased with the time before 10 days after stenting. However, SRSs tended to become steady and even showed a trend of aggravation after that. Second, as for USSQ, visual analogue pain scale was used to evaluate the body pain. To our knowledge, a minimum of 13 mm difference on a 10 cm scale meant a clinically significant pain variation. The rest of the USSQ scales were recorded by discrete score ranged from 1 to 5 according to the severity of patients' subjective symptoms which the difference of every point meant a significant change of symptoms. Third, though we systematically reviewed the additional problems and drug treatment-related side effects, we did not investigate them by network meta-analysis method because of the limited data, which were also important for drug comparison. Subsequent studies could take this into consideration if possible. Fourth, some studies discussing other common drugs such as terazosin [33, 34], doxazosin [25, 35] and tolterodine [13, 34, 35] were excluded in our network meta-analysis because they did not meet our inclusion criteria (not using USSQ). However, further analysis should be performed when the data are enough in the future. Finally, bias caused by certain methodological deficiencies and not well-designed RCTs included in the analysis still existed in our study. All of these had an impact on the interpretation of the results and the related conclusion needed to be carefully treated.

Conclusion

The current network meta-analysis demonstrated that Tam, Alfu, Soli and Tam + Soli provided beneficial effects on SRSs with different efficacy. Combination of Tam and Soli had the highest probability to be the best intervention for

SRSs. As for monotherapy, Soli showed advantages on most respects except for pain relief compared to Tam or Alfu. Tam and Alfu showed similar results on urinary symptoms and body pain relief. However, the results should be interpreted with caution due to the limitations mentioned above.

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Author's contribution JZ and CY: project development, data collection and management, manuscript writing and revising; LQ: data collection, data analysis; LB and YT: data collection, data analysis; LH: data collection, data analysis; WK: project design and development, data interpretation, manuscript editing and revising. All authors read and approved the final manuscript.

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Compliance with ethical standards

Conflict of interest The authors of this article as well as all the included studies declare that they have no conflict of interest.

Ethical standards The study protocol is compliant with ethical standards.

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