COMPARISON OF PHARMACOLOGY AGENTS EFFECT IN TREATING URETERAL STENT RELATED SYMPTOMS: SYSTEMATIC REVIEW & META-ANALYSIS OF RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Objective: *We wish to update existing meta-analyses to assess the effectiveness of pharmacological agents against ureteral stent-related symptoms with better design of RCTs, as well as more valid and reliable measurement methods.* ***Material & Methods:*** *Relevant published articles up to February 2022 were obtained from PubMed, CENTRAL, Google Scholar, Science Direct, and DOAJ. All single-blind or double-blind RCTs with various comparisons using pharmacological agents and/or placebo in patients with ureteral stent-related symptoms, with outcome assessment using USSQ at week 1 and week 4 during stent placement was included in the study. Statistical parameter Mean Difference (MD) with 95% CI was used to measure effect size. The p value less than 0.05 indicates statistical significance.* ***Results:*** *Alpha blockers (2 studies, 85 samples) significantly reduced fourth week UIS compared to placebo (MD: – 5.46, 95% CI: – 7.47 to -3.46, I2 = 0%, P = < 0.001), and alpha blockers (2 studies, 42 samples) significantly reduced first week SIS compared to combination therapy (MD: – 0.82, 95% CI: – 1.56 to – 0.08, I2 = 0%, P = 0.03). The results of the meta-analysis of USSQ scores in other domains have no significant differences.* ***Conclusion:*** *Alpha blockers were better than placebo in reducing UIS due to ureteral stent in the fourth week of stent placement, and better than combination therapy in reducing SIS due to ureteral stent in the first-week post stenting. However, more RCTs are needed with larger samples and better designs to reach valid conclusions.*

Keywords: *Stents, Randomized Controlled Trials as Topic, Single-Blind Method.*

ABSTRAK

Tujuan: *Kami ingin memperbarui meta analisis yang ada untuk menilai efektivitas agen-agen farmakologi terhadap gejala-gejala terkait ureteral stent dengan desain RCT yang lebih baik, serta metode pengukuran yang lebih valid dan reliabel.* ***Bahan & Cara:*** *Artikel terpublikasi sampai Februari 2022 yang relevan diperoleh dari PubMed, CENTRAL, Google Scholar, Science Direct, dan DOAJ. Seluruh RCT jenis single-blind atau double-blind dengan berbagai variasi perbandingan menggunakan agen-agen farmakologi dan/atau plasebo pada pasien-pasien dengan gejala-gejala terkait ureteral stent, dengan penilaian keluaran menggunakan USSQ pada minggu 1 dan minggu 4 selama pemasangan stent dimasukkan ke dalam penelitian. Parameter statistik Mean Difference (MD) dengan IK95% digunakan untuk mengukur size effect. Nilai p lebih kecil dari 0.05 menunjukkan kemaknaan secara statistik.* ***Hasil:*** *Alpha blocker (2 studi, 85 sampel) secara signifikan mengurangi UIS minggu keempat dibanding plasebo (MD: – 5.46, 95% CI: – 7.47 to -3.46, I2 = 0%, P = < 0.001), dan alpha blocker (2 studi, 42 sampel) secara signifikan mengurangi SIS minggu pertama dibandingkan terapi kombinasi (MD: – 0.82, 95% CI: – 1.56 to – 0.08, I2 = 0%, P = 0.03). Adapun hasil meta analisis skor USSQ pada domain lain tidak terdapat perbedaan yang signifikan.* ***Simpulan:*** *Alpha blocker lebih baik dibanding plasebo dalam mengurangi UIS akibat ureteral stent pada minggu keempat pemasangan stent, dan lebih baik dibanding terapi kombinasi dalam mengurangi SIS akibat ureteral stent pada minggu pertama pemasangan stent. Namun, dibutuhkan lebih banyak lagi RCT dengan sampel yang lebih besar dan desain yang lebih baik untuk memperoleh kesimpulan yang valid.*

Kata kunci: *Stent, Uji klinik acak terkendali sebagai topik, metode tersamar tunggal.*

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INTRODUCTION

Since first introduced by Zimskind et a. in 1967, the use of ureteral stents in urological practice had become an inseparable and frequent practice, because of its usefulness in many cases.[1-2] However, Joshi et al found that up to 80% of patients with indwelling ureteral stents experience urinary

symptoms and pain that interfere with daily activities and reduce their quality of life.[3-4] The symptoms reported were frequency (50 - 60%), urgency (57 - 60%), dysuria (40%), incomplete emptying (76%), low back pain (19 - 32%), suprapubic pain (30%), and incontinence (25%).[2,5,6]

Several attempts have been made to reduce ureteral stent-related symptoms, such as improving stent materials, stent design, stent size, and one of them is the use of pharmacological agents.[7] Various meta-analyses of existing randomized clinical trials had been carried out to assess the effectiveness of which pharmacological agent is best for treating ureteral stent-related symptoms, but the results are still contradictory,[8-11] with many randomized clinical trials not using design and measurement methods that are considered valid and reliable.[12-13]

Based on this, we would like to update an existing meta-analysis to assess the effectiveness of pharmacological agents against ureteral stent-related symptoms using randomized clinical trials with better design, best validity and reliable measurement methods to obtain results with less potential for bias.

OBJECTIVE

We wish to update existing meta-analyses to assess the effectiveness of pharmacological agents against ureteral stent-related symptoms with better design of RCTs, as well as more valid and reliable measurement methods.

MATERIAL & METHODS

The study was conducted based on guidelines from the Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA).14 Reviewers (MAM, AAM) independently conducted systematic article searches on PubMed, CENTRAL, Google Scholar, Science Direct, and DOAJ. The search was carried out for research published until February 2022. The literature search strategy was shown in Table 1. Furthermore, references of found articles was searched for missed study. In each stage of article search, double checks are carried out by both reviewers.

Table 1. Search Keywords and Databases.

Database	Keyword	Articles (n)
PubMed	(("ureteral stent related symptoms"[Title/Abstract] OR ((("ureter"[MeSH Terms] OR "ureter"[All Fields] OR "ureteral"[All Fields] OR "ureteric"[All Fields] OR "ureteritis"[All Fields]) AND ("stent s"[All Fields] OR "stentings"[All Fields] OR "stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields] OR "stented"[All Fields] OR "stenting"[All Fields])) AND "associated pain"[Title/Abstract])) AND ("treatment"[Title/Abstract] OR "alpha blocker"[Title/Abstract] OR "anti muscarinic"[Title/Abstract] OR "pde5 inhibitor"[Title/Abstract] OR "beta 3 agonist"[Title/Abstract] OR "NSAID"[Title/Abstract] OR "botulinum toxin"[Title/Abstract] OR "mirabegron"[Title/Abstract] OR "tamsulosin"[Title/Abstract] OR "alfuzosin"[Title/Abstract] OR "silodosin"[Title/Abstract] OR "solifenacin"[Title/Abstract] OR "tolterodine"[Title/Abstract] OR "oxybutynin"[Title/Abstract] OR "ketorolac"[Title/Abstract] OR "tadalafil"[Title/Abstract] OR "sildenafil"[Title/Abstract])) AND (randomizedcontrolledtrial[Filter])	11
Google Scholar	"ureteral stent related symptoms" OR "stent related symptoms" OR “ureteral stent associated pain" AND "treatment" AND "randomized controlled trial"	415
Science Direct	ureteral stent related symptoms AND treatment Using Filter: Research articles	1610
CENTRAL	ureteral stent related symptoms AND treatment	129
DOAJ	ureteral stent related symptoms AND treatment	22

This study included all studies with several inclusion criteria, namely: (i) Randomized Controlled Trials (RCT) with a single-blind or double-blind design, (ii) comparing a pharmacological agent and a placebo, between two types of pharmacological agents, or a combination of pharmacological agents and placebo, in patients with ureteral stent-related symptoms, (iii) assessing outcome using the Ureteral Stent Symptom Questionnaire (USSQ) at first week and fourth week during stent placement, (iv) using 5 assessment domains in USSQ, namely Urinary Index Score (UIS), Pain Index Score (PIS), General Health Index Score (GHIS), Work Index Score (WIS), and Sex Index Score (SIS).

The primary outcome in this study was the difference in mean scores across the 5 assessment domains on the USSQ, where the USSQ was a questionnaire developed to assess the symptoms and effects of ureteral stents on patients' quality of life. USSQ was a valid and reliable instrument as a reference standard for measuring symptoms related to ureteral stents and has undergone language validation in various parts of the world. USSQ assesses 6 arena indix; urinary index, pain index, general health index, work index, sex index, and additional problems.[4] Each index had several questions accompanied by a score. The higher the score on index, the more disturbing the symptoms experienced.[8] In this study, we only assessed 5 USSQ domains.

Data abstraction from studies that met the inclusion criteria was carried out by 2 independent reviewers (AAM, MAM) using a spreadsheet table from Microsoft Excel. Some information was abstracted, namely the characteristics of the RCT, the characteristics of the sample, the definition of the experimental and control groups, the outcome measurement method, and the outcome data of each group.

The validity assessment was carried out independently by two reviewers (AAM, MAM) using the Cochrane Risk of Bias (RoB) tool version 2 for the RCT. If there was a difference of opinion between the first two reviewers, the discussion involves the third (AA) and fourth (MSD) reviewers until consensus reached. Funnel plots were used to assess publication bias of research outcomes.

Statistical analysis using Review Manager (RevMan) software version 5.4. Statistical parameter Mean Difference (MD) with 95% CI was used to measure effect size. Heterogeneity between studies was calculated using I^2. If the value of I^2 is greater than 50%, it is estimated that the heterogeneity of the study is high statistically and pooled statistics using a random effect model. If the value of I^2 is less than 50%, then the pooled statistics used is the fixed effect model. Statistical test using continuous variance. The p value less than 0.05 indicates statistical significance.

RESULTS

The search and screening of articles was systematically carried out based on the PRISMA 2020 flowchart guidelines, as shown in Figure 1.[14]

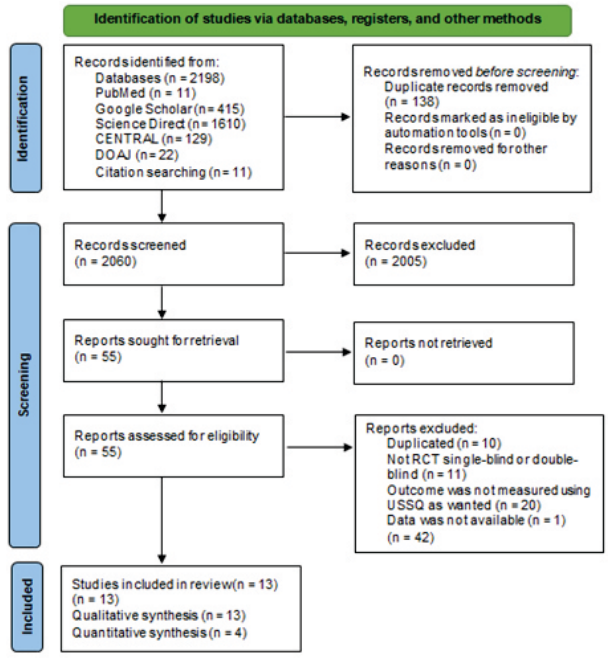


Figure 1. Systematic search dan screening article based on the PRISMA 2020 flow diagram.

From an online database search, 2198 articles were found. After the duplicate articles were excluded, we performed a primary screening on the abstract and title of each article. From the primary screening, we excluded 2005 articles. After that, we conducted secondary screening of all article texts, and obtained a total of 13 articles. In the end, out of 13 articles, 6 articles did not have a comparison in quantitative analysis, 2 articles did not provide the data needed for analysis, and 1 article experienced data skewness in data processing. Thus, only 4 articles were eligible for quantitative analysis. The characteristics of appropriate studies were shown in Table 2.

Table 2. Characteristics of eligible studies.

Study, Year	Design	Total Sample (n)	Intervention	Control	Outcome	Duration of therapy	Follow up	Inclusion criteria
Wang et al., 2009 [16]	RCT, double-blind	154	Tamsulosin 0,4 mg	Placebo	USSQ, IPSS	2 weeks	1st week and 4th week (2 weeks post stent removal)	All patients, age N/A, who underwent URS
Gupta et al., 2010 [27]	RCT, single-blind	51	3 periureteral 1 ml injections of Botulinum toxin (BTX) at a concentration of 10 U/ml (total 30 units of BTX)	Blank	USSQ, VAS, narcotic log sheet	1 week	7th day post ureteral stenting	All patients aged 19 - 81 years who required a unilateral stent for benign pathology (nephrolithiasis, ureteral strictures, surveillance ureteroscopy, etc.)
Singh et al., 2014 [17]	RCT, double-blind	60	Tamsulosin 0,4 mg	Placebo	USSQ, IPSS, VAS	4 weeks	at 3rd day, 2nd, 4th, 6th, and 8th week (stent removal at 6th week)	All patients aged 18 - 80 years who underwent PCNL and URS
Dellis et al., 2014 [18]	RCT, double-blind	150	Alfuzosin 10 mg, Tamsulosin 0,4 mg	Placebo	USSQ	4 weeks	1st and 4th week post ureteral stenting, 4th week post stent removal	All patients aged 17 - 81 years who underwent ESWL and URS
Sivalingam et al., 2016 [22]	RCT, double-blind	80	Tamsulosin 0,4 mg + Tolterodine ER 4 mg, Tamsulosin 0,4 mg + Placebo	Blank	USSQ	1 week	Before stenting in the surgery day (T0), the morning post stenting (T1), 7th day post stenting/morning of stent removal (T2), the day post stent removal (T3)	All patients aged > 18 years who underwent URS
Maldonado-Avila et al., 2016 [20]	RCT, single-blind	51	Tamsulosin 0,4 mg, Oxybutynin 5 mg, Tamsulosin 0,4 mg + Oxybutynin 5 mg	Blank	USSQ	3 weeks	7th and 21st day post ureteral stenting	All patients aged > 18 years who-underwent URS
Dellis et al., 2017 [19]	RCT, double-blind	260	Tamsulosin 0,4 mg, Solifenacin 5 mg, Tamsulosin 0,4 mg + Solifenacin 5 mg	Placebo	USSQ	4 weeks	1st and 4th week post ureteral stenting, 4th week post stent removal	All patients aged 17 - 84 years who underwent ESWL, URS, and had unilateral hydronephrosis for any reason
Jo et al., 2018 [28]	RCT, double-blind	92	Hyaluronic acid 800 mg/ Chondroitin sulfate 1 g intravesical instillation	Placebo	USSQ, IPSS, VAS	2 hours	7th day post ureteral stenting	All patients aged = 18 years who underwent URS
Farshi Harghro et al., 2019 [26]	RCT, double-blind	72	Tadalafil 10 mg	Placebo	USSQ	4 weeks	4th weeks post ureteral stenting and intervention	Male patients aged 15 - 70 years with an indication for unilateral ureteral stent
Palinggi et al., 2020 [24]	RCT, double-blind	50	Solifenacin 5 mg, Mirabegron 50 mg	Blank	USSQ	3 weeks	7th, 14th, 21st, 28th day post ureteral stenting	All patients aged 18 - 79 years who underwent URS, PCNL, or ESWL
Ilyas et al., 2021 [25]	RCT, double-blind	50	Tadalafil 10 mg, Tamsulosin 0,4 mg	Blank	USSQ	3 weeks	7th, 14th, 21st, 28th day post ureteral stenting	All patients aged 18 - 79 years who-underwent URS or ESWL
Hasbi et al., 2021 [21]	RCT, double-blind	50	Tamsulosin 0,4 mg, Tamsulosin 0,4 mg + Solifenacin 5 mg	Blank	USSQ	3 weeks	7th, 14th, 21st, 28th day post ureteral stenting	All patients aged 20 - 60 years who underwent URS
Yavuz et al., 2021 [23]	RCT, single-	161	Tamsulosin 0,4 mg, Mirabegron	Placebo	USSQ	4 weeks	4 weeks post ureteral stenting	All patients aged > 18 years who underwent URS

N/A = not applicable

The risk analysis of bias showed that the most common bias in the included studies was due to intended interventions, not blinding aspects, but mostly due to not conducting an intention to treat (ITT) analysis, which is the best type of analysis for RCTs. Next, the bias arising from the randomization process and the bias in selections of the reported results. In this aspect, most articles do not present the randomization process, concealment, or RCT protocol. However, we continue to make judgments based on assumptions about the quality of the journals in which they were published, the size of clinical trials, and the experience of researchers in conducting clinical trials.[15] Figure 2 presents the risk of bias assessment of each study. An assessment of publication bias was carried out using funnel plots which showed some publication bias, as shown in Figure 3.

Table 3. Comparison of pharmacological agents in reducing ureteral stent-related symptoms.

Comparison	Study, Year	Intervention	Result
Alpha-blocker vs Placebo	Wang et al., 2009	Tamsulosin 0,4 mg vs Placebo	The tamsulosin group showed a significant difference from the placebo in reducing UIS, PIS, and GHIS at week 1 post stenting. When comparing week 1 and week 4 of evaluation, both groups showed significant worsening of UIS, PIS, GHIS, and WIS, except SIS. The mean score of quality of life in IPSS is better in tamsulosin than in the placebo group.
	Singh et al., 2014	Tamsulosin 0,4 mg vs Placebo	The tamsulosin group demonstrated a significant decrease in UIS, PIS, WIS, VAS score in the loin area, flank, and suprapubic area, average VAS score, need for antibiotics, and the number of hospital visits (p = < 0,05) at the end of the fourth weeks. Decreases in other values were also observed, albeit insignificant.
	Dellis et al., 2014	Alfuzosin 10 mg vs Placebo, Tamsulosin 0,4 mg vs Placebo	The alpha-blocker group demonstrated an overall statistically significant lower UIS (p = < 0,001), PIS (p = < 0,001 with stent in situ), and GHIS (p = < 0,002) than the placebo group. SIS and QoL were also positively influenced. There was no difference in various outcomes between the 2 alpha-blockers.
	Dellis et al., 2017	Tamsulosin 0,4 mg vs Placebo	In the first cohort*, patients on either tamsulosin or solifenacin expressed a significantly lower UIS, PIS, GHIS (p = < 0,001, p = 0,002, p = < 0,001 with stent in situ, respectively) than placebo. SIS was only significantly reduced in the post-stenting period (p = 0,006), and WIS was significantly reduced only in the 4th week (p = 0,021). In the second cohort*, the combination group showed a significant improvement in UIS and PIS in the 4th week after stenting (p = < 0,001 and p = < 0,001, respectively), and WIS after stent removal (p = 0,001), compared to the monotherapy or placebo group, with no significant improvements in other USSQ sections.
	Yavuz et al., 2021	Tamsulosin 0,4 mg vs Placebo	The doses of analgesic usage were significantly lower in the tamsulosin and mirabegron group compared to the placebo group (p = < 0,001). UIS was also significantly lower in the tamsulosin group than in the placebo group (p = 0,001). However, the other index scores were similar between the groups.
Alpha-blocker vs Alpha-blocker	Dellis et al., 2014	Alfuzosin 10 mg vs Tamsulosin 0,4 mg	S/A
Alpha-blocker vs Anti-muscarinic	Maldonado-Avila et al., 2016	Tamsulosin 0,4 mg vs Oxybutynin 5 mg,	The combination group demonstrated a better result in reducing UIS (p = < 0,001), WIS (p = 0,049), SIS (p = 0,03), and additional problems index score (p = 0,03) than the tamsulosin and oxybutynin group. No significant difference was observed among PIS and GHIS.
	Dellis et al., 2017	Tamsulosin 0,4 mg vs Solifenacin 5 mg	S/A
Alpha-blocker vs Beta-3-agonist	Yavuz et al., 2021	Tamsulosin 0,4 mg vs Mirabegron 50 mg	S/A
Alpha-blocker vs PDE5 inhibitor	Ilyas et al., 2021	Tamsulosin 0,4 mg vs Tadalafil 10 mg	Overall, both treatment groups had a good effect in reducing the USSQ score, with significantly better results in the tadalafil group compared to the tamsulosin group, except in UIS week 2 and GHIS weeks 2 and 4
Alpha-blocker vs Combination*	Maldonado-Avila et al., 2016	Tamsulosin 0,4 mg vs Tamsulosin 0,4 mg + Oxybutynin 5 mg	S/A
	Sivalingam et al., 2016	Tamsulosin 0,4 mg + Placebo vs Tamsulosin 0,4 mg + Tolterodine ER 4 mg,	Both groups showed no significant difference in UIS, PIS, GHIS, WIS, and SIS from T1 and T2.
	Dellis et al., 2017	Tamsulosin 0,4 mg vs Tamsulosin 0,4 mg + Solifenacin 5 mg	S/A
	Hasbi et al., 2021	Tamsulosin 0,4 mg vs Tamsulosin 0,4 mg + Solifenacin 5 mg	Both treatment groups showed an improvement in PIS and WIS variables, with the combination group showing better improvement in UIS and SIS variables than the monotherapy group in the 2nd to 4th week of therapy. Also, the combination group showed better improvement in GHIS and additional problems index score only in the 4th week

S/A: Same as above
*The combination therapy consists of alpha-blocker and anti-muscarinic

In this study, we found 13 studies that met the inclusion criteria, with various comparisons of pharmacological agents and their results shown in Table 3. In a comparison of alpha-blockers vs placebo, Wang et al,[16] Singh et al,[17] and Dellis et al18 concluded that tamsulosin therapy was better at reducing ureteral stent related symptoms than placebo, with Dellis et al[18] specifically comparing

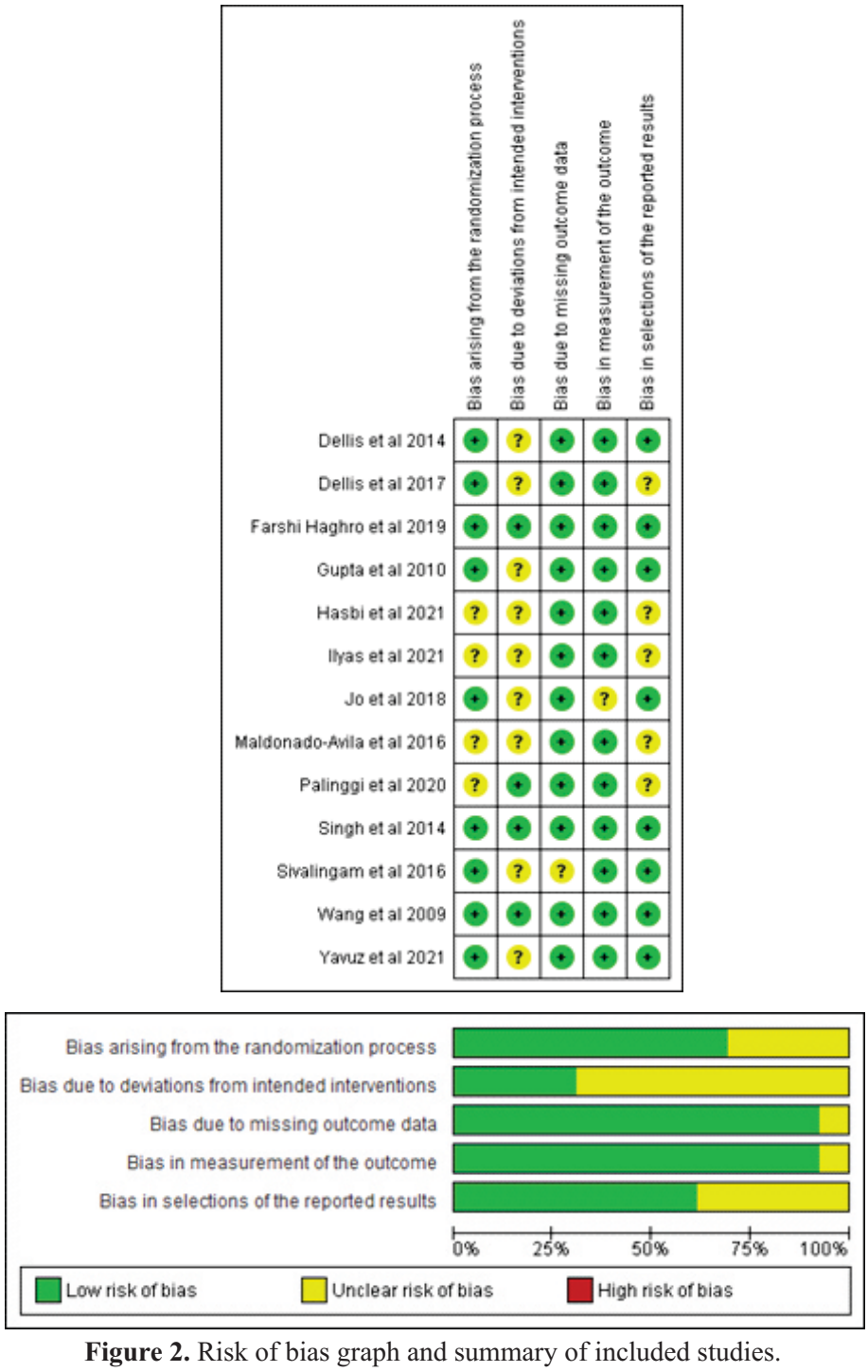


Figure 2. Risk of bias graph and summary of included studies.

the two Types of alpha blockers, namely tamsulosin and alfuzosin, reported that both types of alpha blockers were equally good at reducing ureteral-stent related symptoms.

Dellis et al,[19] Maldonado Avila,[20] and Hasbi et al[21] in their study concluded that combination therapy using alpha-blockers and anti-muscarinic was better at reducing ureteral stent-related symptoms than monotherapy using alpha-blockers, anti-muscarinic, or placebo. This was not in line with the results of Sivalingam et al22 who reported that the use of tamsulosin or the combination of tamsulosin and tolterodine was not beneficial in reducing ureteral stent related symptoms. However,

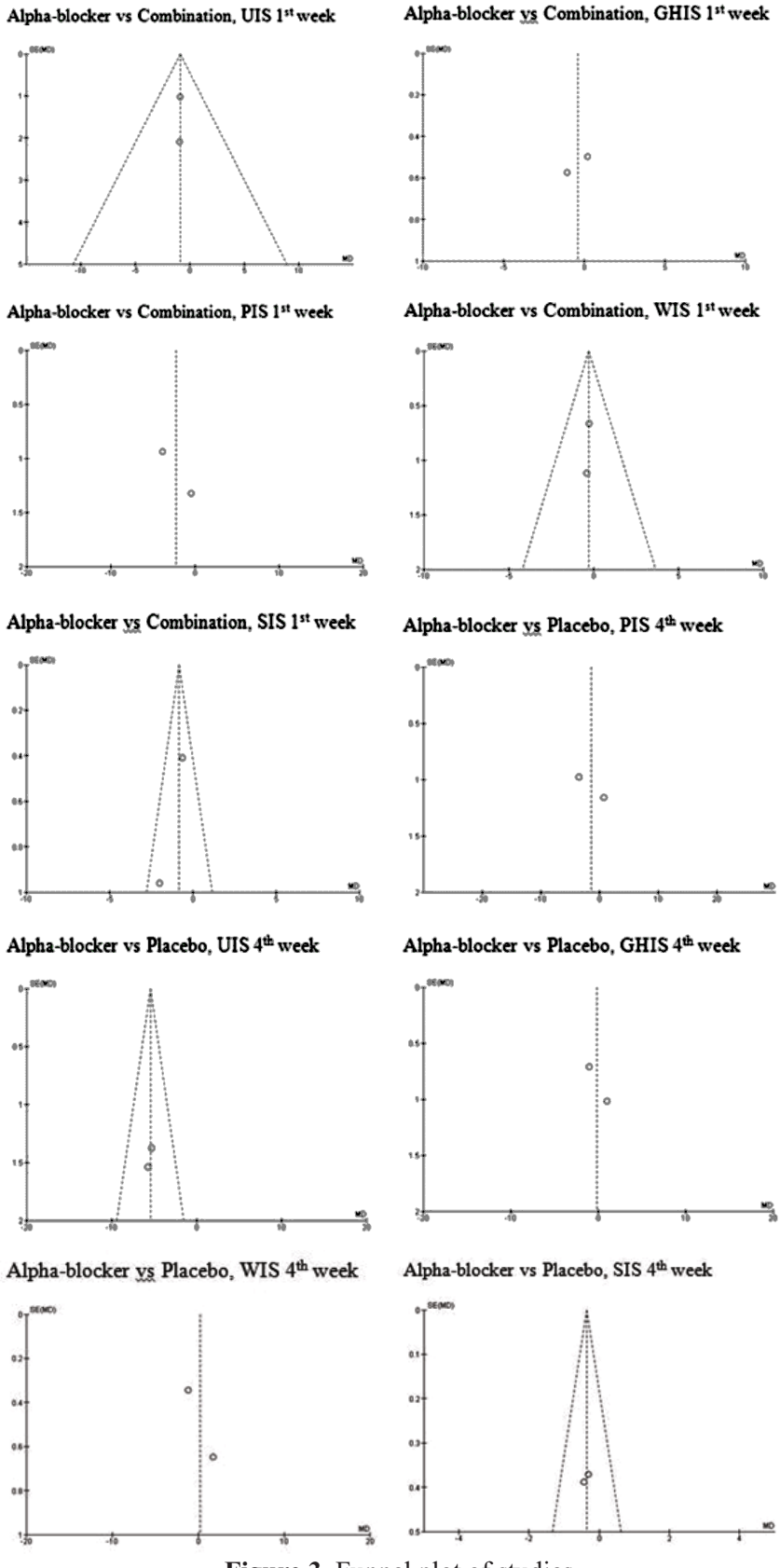
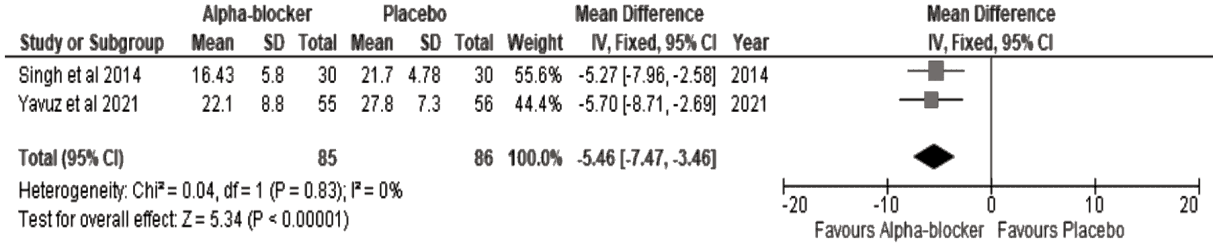
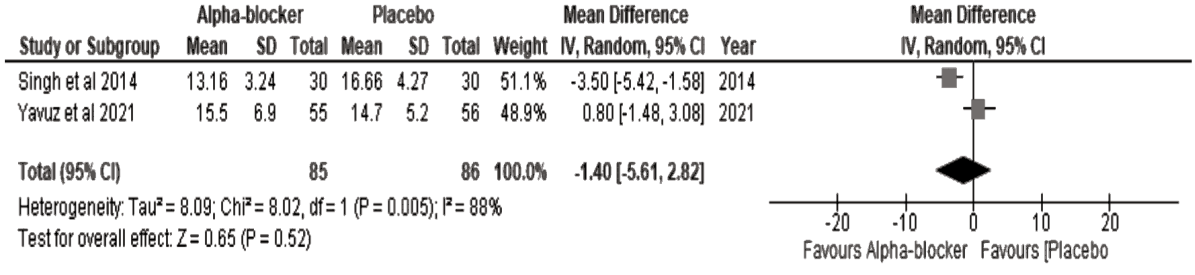


Figure 3. Funnel plot of studies.

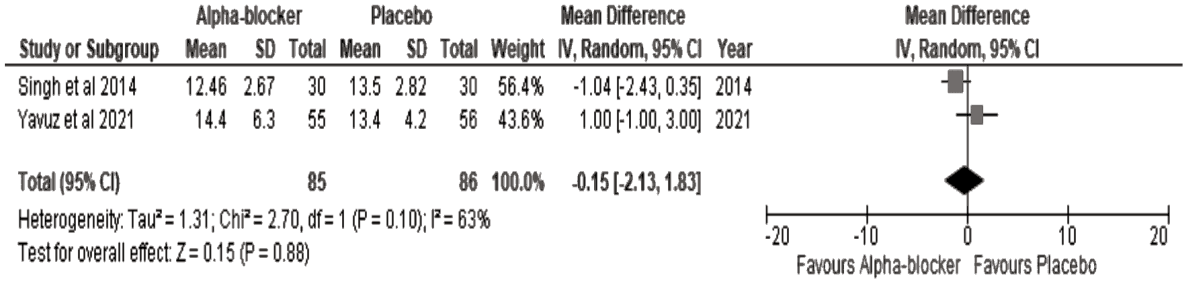
UIS



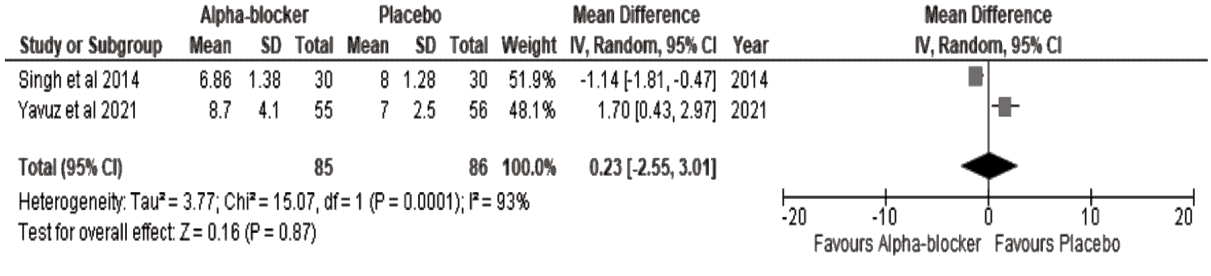
PIS



GHIS



WIS



SIS

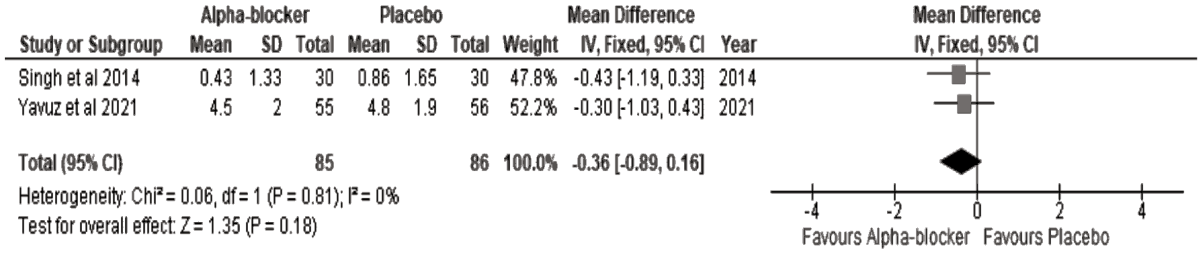
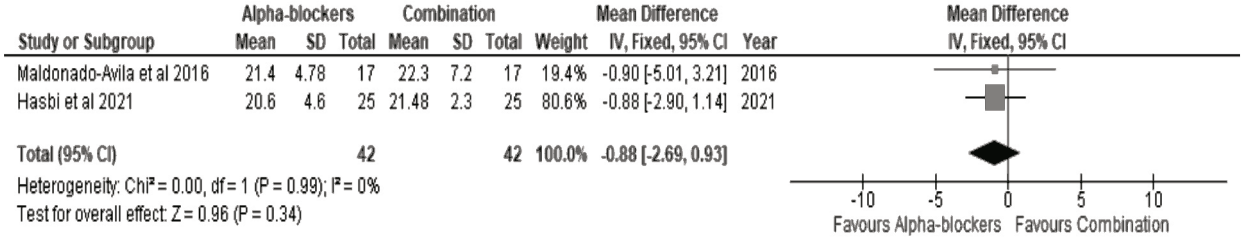
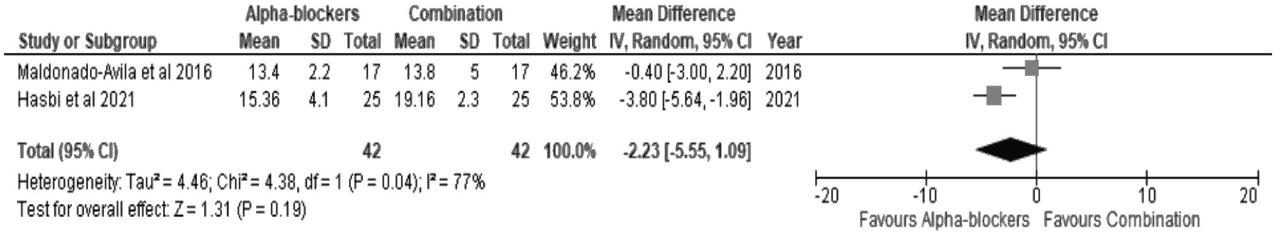


Figure 4. Forest plot of USSQ assessment at 4th week after stenting with alpha-blocker treatment compared to placebo.

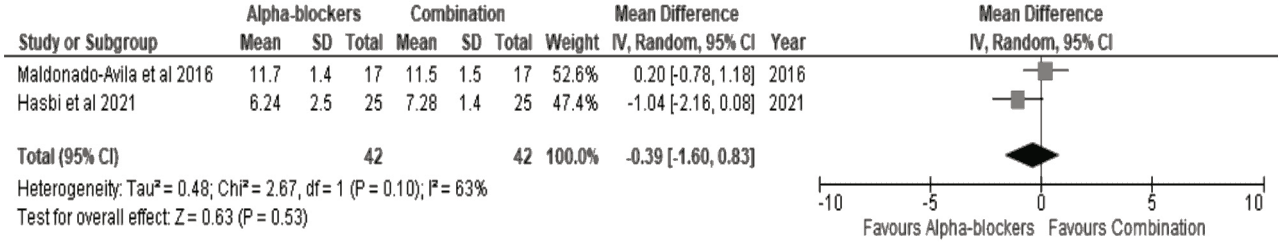
UIS



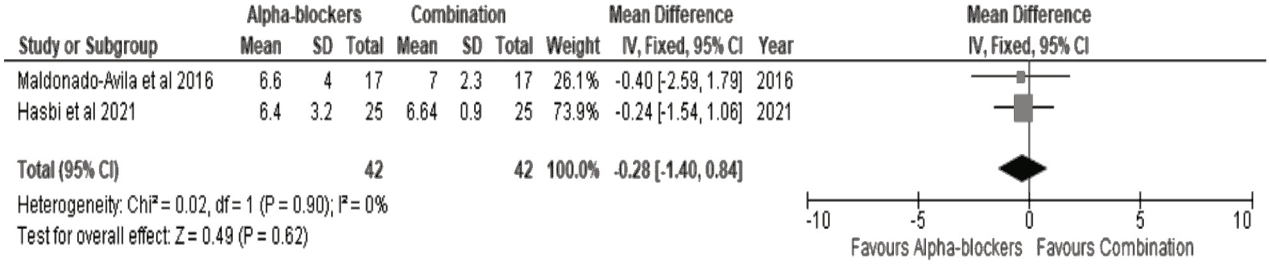
PIS



GHIS



WIS



SIS

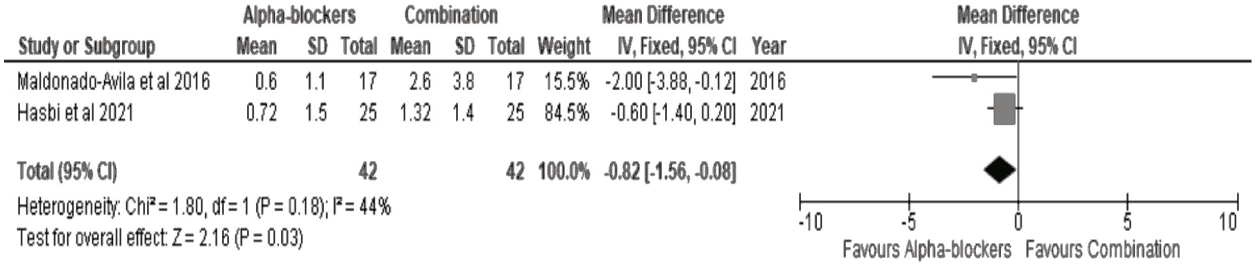


Figure 5. Forest plot of USSQ assessment at 1st week after stenting with alpha-blocker treatment compared to combination treatment.

this may be due to the shorter outcome assessment time frame in Sivalingam et al's study compared to other studies, so that the possible optimal therapeutic window of the studied drug has not been achieved. In their research, Dellis et al[19] and Hasbi et al[21] used a combination of tamsulosin and solifenacin, while Maldonado-Avila et al[22] used a combination of tamsulosin and oxybutynin.

Yavuz et al[23] reported that tamsulosin and mirabegron were less effective in treating ureteral stent related symptoms, because they only reduced analgesic use compared to placebo, with tamsulosin only reducing urinary symptoms on USSQ.

Palinggi et al[24] reported that there were no significant effect of solifenacin or mirabegron in reducing ureteral stent-related symptoms.

Ilyas et al[25] who tested the effect of PDE5 inhibitor agents, namely tadalafil reported that treatment with tadalafil was better than tamsulosin, while Farshi Haghro et al[26] with the same drug agent also reported that tadalafil was better than placebo in treating ureteral stent related symptoms.

Gupta et al[27] reported that the use of periureteral BTX injection reduced VAS and analgesic requirements after ureteral stent placement, but did not reduce the patient's irritating symptoms on the USSQ score. Jo et al[28] reported that the use of high concentrations of HA/CS was effective in improving urinary complaints and pain after ureteral stent placement and reducing the need for additional medication or procedures compared to placebo.

Of the 13 included studies, 3 studies recommended the use of alpha blockers, namely tamsulosin and alfuzosin to reduce ureteral stent related symptoms, 3 studies recommended the use of combination therapy with alpha-blockers and anti-muscarinic. 3 studies concluded that therapy using alpha-blockers, anti-muscarinic, beta-3 agonists, or a combination using alpha-blockers and anti-muscarinic did not provide benefits. 2 studies recommend the use of a PDE5 inhibitor, namely tadalafil to reduce ureteral-stent-related symptoms. 1 study concluded the use of periureteral BTX injection is not very effective but has good potential in the future. 1 study concluded that the use of high concentrations of HA/CS could reduce ureteral stent-related symptoms well.

The results of a meta-analysis of 2 studies using 85 samples, showed that alpha blockers reduced the fourth week UIS significantly compared to placebo (MD: - 5.46, 95% CI: - 7.47 to -3.46, I2 = 0%, P = < 0.001). The results of the meta-analysis of USSQ scores in other domains showed no significant differences, as shown in Figure 4.

Pooled meta-analysis results from 2 studies using 42 samples, showed that alpha blockers significantly reduced first week SIS compared to combination therapy (MD: - 0.82, 95% CI: - 1.56 to - 0.08, I2 = 0 %, P = 0.03). The results of the meta-analysis of USSQ scores in other domains showed no significant differences, as shown in Figure 4.

DISCUSSION

Based on the inclusion criteria, we were only able to compare alpha blockers and placebo in the fourth post stenting week, and compared alpha blockers and a combination of alpha-blockers and anti-muscarinics in the first week post stenting. The results of our meta-analysis were Alpha blockers were only significantly better than combination therapy in reducing SIS in the first week post stenting (P = 0.03), and only better than placebo in reducing UIS in the fourth week post stenting (P = < 0.001). These results are inconsistent with a meta-analysis of 1350 patients conducted by Deliveliotis et al8 which concluded that compared with placebo, alpha-blockers significantly reduced UIS, GHIS, and WIS at the fourth post stenting week, not PIS, and SIS. Likewise, the results of a meta-analysis of 1489 samples conducted by He et al[29] concluded that alpha-blockers significantly reduced UIS, PIS, GHIS, and SIS at the fourth post stenting week, but not WIS.

As for the comparison between alpha-blockers and combinations of alpha-blockers and anti-muscarinics in the first week post stenting, the results of our meta-analysis are also not in line with the meta-analysis conducted by Chen et al[30] on 238 samples which found, there were no significant difference between the group in reducing UIS, GHIS, WIS, SIS, and USSQ total score, except tamsulosin monotherapy was significantly better in reducing PIS in the first week post stenting.

The advantage of our study that based on our knowledge, this is the first systematic review and meta-analysis to assess the effectiveness of a pharmacological agent in treating ureteral stent-related symptoms by only including blinded-RCTs in the review from the start, so the potential bias in our results is less. Even so, this may also cause differences with the results of the meta-analysis obtained previously.

In addition, the outcome assessment criteria used the USSQ at week 1 and week 4 of stenting. Although Joshi et al (4) also suggested the use of USSQ at 4 weeks post removal stenting, we did not include it in our meta-analysis, because we only wanted to focus on the effect of pharmacologic agents at the time of stenting, according to how the patient's complaints were experienced in daily practice when the stent is attached.

Although there were advantages, but on the other hand this also produces some shortfall. First, we found publication bias in funnel plots, Second, due to the stringent selection of inclusion criteria, resulting in the few RCTs that were included, the sample size in the review was relatively small. These raise questions about the strength of the meta-analysis. This small sample also made us unable to compare the various available pharmacological agents and the various outcome periods in the first week and fourth week post stenting according to the criteria proposed by Joshi et al, because most of the existing RCT studies still use the USSQ assessment which is not in accordance with Joshi et al4 criteria. So, the results from our meta-analysis were not able to answer how effective a pharmacological agent was at various stenting periods.

Therefore, we strongly recommend that in the future, more RCTs should be carried out that not only pay attention to larger samples and multicenter, but also with good design and outcome assessment using USSQ which is accordance with the proposed standards.

CONCLUSION

Alpha blockers were better than combination therapy in treating sexual symptoms due to ureteral stent in the first week post placement, and better than placebo in treating urinary symptoms due to ureteral stent in the fourth week of stent placement. However, more RCTs are needed with larger samples and better designs to reach valid conclusions.

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