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.

INTRODUCTION

Since first introduced by Zimskind et al. 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. 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%).

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. 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, with many randomized clinical trials not using design and measurement methods that are considered valid and reliable.

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). 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>
<thead>
<tr>
<th>Database</th>
<th>Keyword</th>
<th>Articles (n)</th>
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<tbody>
<tr>
<td>Google Scholar</td>
<td>&quot;ureteral stent related symptoms&quot; OR &quot;stent related symptoms&quot; OR &quot;ureteral stent associated pain&quot; AND &quot;treatment&quot; AND &quot;randomized controlled trial&quot;</td>
<td>415</td>
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<td>Science Direct</td>
<td>ureteral stent related symptoms AND treatment</td>
<td>1610</td>
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<td>CENTRAL</td>
<td>ureteral stent related symptoms AND treatment</td>
<td>129</td>
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<td>DOAJ</td>
<td>ureteral stent related symptoms AND treatment</td>
<td>22</td>
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</table>
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 index; urinary index, pain index, general health index, work index, sex index, and additional problems. Each index had several questions accompanied by a score. The higher the score on index, the more disturbing the symptoms experienced. 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 $\Gamma$. If the value of $\Gamma$ 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 $\Gamma$ 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.

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.
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. 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.

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Study, Year</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-blocker vs Placebo</td>
<td>Wang et al., 2009</td>
<td>Tamsulosin 0.4 mg vs Placebo</td>
<td>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.</td>
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<tr>
<td></td>
<td>Singh et al., 2014</td>
<td>Tamsulosin 0.4 mg vs Placebo</td>
<td>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 = &lt; 0.05) at the end of the fourth week. Decreases in other values were also observed, albeit insignificant.</td>
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<td></td>
<td>Dellis et al., 2014</td>
<td>Alfuzosin 10 mg vs Placebo, Tamsulosin 0.4 mg vs Placebo</td>
<td>The alpha-blocker group demonstrated an overall statistically significant lower UIS (p = &lt; 0.001), PIS (p = &lt; 0.001 with stent in situ), and GHIS (p = &lt; 0.001) than the placebo group. SIS and QoL were also positively influenced. There was no difference in various outcomes between the 2 alpha-blockers.</td>
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<tr>
<td></td>
<td>Dellis et al., 2017</td>
<td>Tamsulosin 0.4 mg vs Placebo</td>
<td>In the first cohort*, patients on either tamsulosin or solifenacin expressed a significantly lower UIS, PIS, GHIS (p = &lt; 0.001, p = &lt; 0.001, p = &lt; 0.001 with stent in situ, respectively) than placebo. SIS was only significantly reduced in the post-stent 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 = &lt; 0.001 and p = &lt; 0.001, respectively), and WIS after stent removal (p = &lt; 0.001), compared to the monotherapy or placebo group, with no significant improvements in other USSQ sections.</td>
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<tr>
<td></td>
<td>Yavuz et al., 2021</td>
<td>Tamsulosin 0.4 mg vs Placebo</td>
<td>The doses of analgesic usage were significantly lower in the tamsulosin and mirabegron group compared to the placebo group (p = &lt; 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.</td>
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<tr>
<td>Alpha-blocker vs Alpha-blocker</td>
<td>Dellis et al., 2014</td>
<td>Alfuzosin 10 mg vs Tamsulosin 0.4 mg</td>
<td>S/A</td>
</tr>
<tr>
<td>Alpha-blocker vs Anti-muscarinic</td>
<td>Maldonado-Avila et al., 2016</td>
<td>Tamsulosin 0.4 mg vs Oxybutynin 5 mg</td>
<td>The combination group demonstrated a better result in reducing UIS (p = &lt; 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.</td>
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<td></td>
<td>Dellis et al., 2017</td>
<td>Tamsulosin 0.4 mg vs Solifenac 5 mg</td>
<td>S/A</td>
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<td>Alpha-blocker vs Beta-3-agonist</td>
<td>Yavuz et al., 2021</td>
<td>Tamsulosin 0.4 mg vs Mirabegron 50 mg</td>
<td>S/A</td>
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<td>Alpha-blocker vs PDE5 inhibitor</td>
<td>Ilyas et al., 2021</td>
<td>Tamsulosin 0.4 mg vs Tadalafil 10 mg</td>
<td>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</td>
</tr>
<tr>
<td>Alpha-blocker vs Combination*</td>
<td>Maldonado-Avila et al., 2016, 2017</td>
<td>Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg + Oxybutynin 5 mg + Placebo vs Tamsulosin 0.4 mg + Tolterodine ER 4 mg, Tamsulosin 0.4 mg vs Tamsulosin 0.4 mg + Solifenac 5 mg</td>
<td>Both groups showed no significant difference in UIS, PIS, GHIS, WIS, and SIS from T1 and T2.</td>
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<td></td>
<td>Sivalingam et al., 2016</td>
<td>Tamsulosin 0.4 mg + Placebo vs Tamsulosin 0.4 mg + Tolterodine ER 4 mg</td>
<td>S/A</td>
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<tr>
<td></td>
<td>Dellis et al., 2017</td>
<td>Tamsulosin 0.4 mg vs Solifenac 5 mg</td>
<td>S/A</td>
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<tr>
<td></td>
<td>Hasbi et al., 2021</td>
<td>Tamsulosin 0.4 mg vs Mirabegron 50 mg</td>
<td>S/A</td>
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</table>

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 al.18 concluded that tamsulosin therapy was better at reducing ureteral stent related symptoms than placebo, with Dellis et al.18 specifically comparing...
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,20 Maldonado Avila,21 and Hasbi et al22 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 tolerodine was not beneficial in reducing ureteral stent related symptoms. However,
Figure 3. Funnel plot of studies.
Figure 4. Forest plot of USSQ assessment at 4th week after stenting with alpha-blocker treatment compared to placebo.
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 and Hasbi et al used a combination of tamsulosin and solifenacin, while Maldonado-Avila et al used a combination of tamsulosin and oxybutynin. Yavuz et al 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 reported that there were no significant effect of solifenacin or mirabegron in reducing ureteral stent-related symptoms. Ilyas et al who tested the effect of PDE5 inhibitor agents, namely tadalaflil reported that treatment with tadalaflil was better than tamsulosin, while Farshi Haghro et al with the same drug agent also reported that tadalaflil was better than placebo in treating ureteral stent related symptoms.

Gupta et al 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 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-muscarinics. 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 tadalaflil 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 al 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 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 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.

REFERENCES


