Preoperative alpha-blockers to facilitate ureteral access sheath (UAS) insertion: a systematic review and meta-analysis

Muhlis Yusuf1,2, Niwanda Yogiswara1,2, Muhammad Rifki Setiawan1,2, Sirin Salsabila1,2, Mohammad Ayodhia Soebadi1,3, Soetojo Wirjopranoto1,2*

ABSTRACT

Background: Recent studies have proposed the use of preoperative alpha-blockers to facilitate urethral access sheath (UAS) placement, but the definite role of this practice is still unclear. We aimed to evaluate the efficacy and safety of alpha-blocker use for UAS placement in intrarenal endoscopic procedures.

Methods: The course of this study followed the preferred reporting items for systematic review and meta-analyses guidelines. Articles investigating the use of preoperative alpha-blockers for patients who underwent intrarenal endoscopic procedures were systematically reviewed from PubMed, EMBASE, and Scopus databases. Odds ratio (OR) with 95% confidence intervals (CIs) were applied for the outcome estimates. Analyses were performed with RevMan 5.4 software. The protocol of this study is enlisted in the registry of PROSPERO (CRD42022342811).

Results: Six articles comprising 462 study populations were included in the review. Meta-analysis on the success rate of UAS placement showed a significant advantage of the alpha-blocker group compared to the control group (OR: 3.83; 1.83-8.00; 95% CI; p = 0.0004). Ureteral wall trauma was higher in the control group (OR: 0.38; 0.17-0.84; 95% CI; p = 0.02). Furthermore, there was no clear association between the UAS size and the success rate of UAS insertion.

Conclusion: Preoperative alpha-blockers may increase the success rate of UAS insertion while decreasing the risk of ureteral wall injury in intrarenal endoscopic procedures.

Keywords: alpha-blockers, ureteral access sheath, flexible ureterorenoscopy, retrograde intrarenal surgery.

INTRODUCTION

There has been an increase in technological advances for renal stone management. Among many new procedures and techniques, retrograde intrarenal surgery (RIRS) is one of the most popular ones. The procedure combines a flexible ureteroscope and lithotripter to treat renal stones.1 Previously, it was recommended for stones that are only 2 cm or smaller, however, many recent reports suggest that it can also be successfully used on stones that are larger than 2 cm.2 With time, auxiliary instruments have been developed to improve the procedure. These improvements involve the utilization of new guidewires, dilators, basket catheters, and ureteral access sheaths (UAS).3 During the procedure, UAS provides easy access to the upper urinary system. It is used for multiple re-entries of instruments to the ureter and collecting system, decreasing intrarenal pressure, and accelerating liquid flow, thus decreasing the risk of bleeding due to vision distortion.4 However, sheath placement remains challenging for some urologists and it carries several risks, such as ureteral trauma, infection, and ureteral stricture.5

Successful placement of UAS relies on the friction of the sheath and ureteral surfaces. Several studies have suggested hydrophilic coatings, balloon dilation, and prior stent placement to decrease the risks. Nevertheless, primary access is sometimes difficult and often leads to excessive force, causing injury to the ureter.6 The failure rate of ureteroscopy due to impassable ureter is approximately 10% and around 22% of patients failed UAS placement.7 Recent studies have proposed the use of alpha-blocker drugs to facilitate UAS placement. Based on the presence of alpha-1 receptors in the distal ureter, the drug is expected to be able to reduce ureteral peristalsis and intraluminal pressure by relaxing and dilating the intramural walls, thus facilitating UAS placement.8 However, the definite role of pre-operative alpha-blockers remains unclear and controversial as existing studies have reported various findings. This systematic review and meta-analysis aimed to evaluate the efficacy and safety of alpha-blocker use for UAS placement in intrarenal endoscopic procedures.
Methods

Study Design
This systematic review and meta-analysis study investigates the difference in success rates and ureteral trauma incidence among patients given preoperative alpha-blockers compared to patients given a placebo before UAS insertion. This study uses a quantitative method following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2020 protocol. AMSTAR-2 checklist is used as a critical appraisal tool to aid the methodological quality of this study.

Systematic Search Strategy
In order to establish the scope classification criteria used in this systematic review and meta-analysis, the PICO (Participants, intervention, comparison, and outcome) of the study was pre-determined. The participants are post-ureteroscopy patients who underwent UAS insertion. The intervention was the administration of preoperative alpha-blockers, while the comparative group was given a placebo. Two outcomes were evaluated in this study; the success rate of UAS placement and ureteral wall trauma incidence. The search for included studies was conducted on Pubmed, Embase, and Scopus databases using the keywords as listed in Table 1. The protocol of this study was registered on PROSPERO (CRD42022342811).

Eligibility Criteria
The inclusion criteria of this study are; randomized controlled trial (RCT) studies, case-control, retrospective cohort, and prospective cohort studies; comparing preoperative alpha-blocker and placebo or no drug administration; research subjects in post-ureteroscopy; accessible articles via Pubmed, Embase, and Scopus. Non-English articles, experimental studies on animals, and unpublished articles were considered ineligible and thus excluded in the process.

Data Extraction
Data extraction was performed by two authors independently. The third author will discuss any differences in the data extraction results. The data extracted were the alpha-blocker administration protocol, duration of administration, average age, number of participants, type of procedure performed, size of UAS, outcomes assessed, and success rate. The success rate is defined as the ureteral stent placement from the insertion site to the kidney and the bladder. On the other hand, ureteral wall trauma in this study was observed using ureteroscopy and assessed by the surgeon.

Quality Assessment
Quality assessment is carried out by evaluating the risk of bias using Cochrane Risk of Bias Tool 2.0. It assessed five domains, including the randomization process, bias due to deviation from the intervention, bias from incomplete outcome data, bias from outcome measurement methods, and bias from outcome selection and reporting. Meanwhile, in observational studies such

<table>
<thead>
<tr>
<th>Table 1. Keywords for study search.</th>
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<tr>
<td><strong>Database</strong></td>
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<td>PubMed/MEDLINE</td>
</tr>
<tr>
<td>EMBASE</td>
</tr>
<tr>
<td>Scopus</td>
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</table>

Figure 1. PRISMA Flow Diagram.
### Baseline characteristic of each study.

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<th>No.</th>
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<th>Study Design</th>
<th>Group</th>
<th>Protocol</th>
<th>Duration</th>
<th>Age (year)</th>
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<th>Procedure Type</th>
<th>UAS Size</th>
<th>Outcome</th>
<th>Success Rate (%)</th>
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<td>Intervention</td>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>No intervention</td>
<td>NR</td>
<td>NR</td>
<td>38</td>
<td>F-URS</td>
<td>12/14 Fr</td>
<td>Success Rate</td>
<td>97%</td>
</tr>
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<td>2</td>
<td>Erturhan</td>
<td>Turkey</td>
<td>Retrospective</td>
<td>Intervention</td>
<td>Tamsulosin 0.4mg</td>
<td>2 weeks</td>
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<td>23</td>
<td>F-URS</td>
<td>9.5/11.5 Fr</td>
<td>Success Rate</td>
<td>65%</td>
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<td></td>
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<td>38.48</td>
<td>25</td>
<td>F-URS</td>
<td>9.5/11.5 Fr</td>
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<td>Intervention</td>
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<td>10 days</td>
<td>43.32</td>
<td>38</td>
<td>F-URS</td>
<td>NR</td>
<td>Success Rate</td>
<td>97%</td>
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<tr>
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<td></td>
<td></td>
<td></td>
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<td>No intervention</td>
<td>10 days</td>
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<td>F-URS</td>
<td>NR</td>
<td>Success Rate</td>
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<td></td>
<td></td>
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<td>11/13 Fr</td>
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<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>No intervention</td>
<td>6 days</td>
<td>60</td>
<td>41</td>
<td>F-URS</td>
<td>12/14 Fr</td>
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<td>Intervention</td>
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<td>58.6</td>
<td>40</td>
<td>37</td>
<td>PCNL</td>
<td>11/14/16 Fr</td>
<td>Success Rate, Ureteral wall injury</td>
<td>41%</td>
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**Systematic search results**

The six articles included in the study consisted of three RCT study designs and three retrospective observational studies with a total of 462 study populations. The average age of the patients in each group ranged from 38.48 to 60.5 years old. Each study intervention includes alpha-blocker administration protocol, i.e. tamsulosin or silodosin. The control group consisted of patients who underwent UAS insertion or intervention. The intervention duration ranged from 2 weeks to 10 days.

**Baseline characteristics of the included studies**

A total of six final articles were included, after applying search strategies to online databases. Initial identification resulted in 94 articles which were then reduced to 46 after exclusion criteria were applied for eligibility. Furthermore, single-arm articles were excluded for eligibility. The outcomes will be presented as forest plots.
without alpha-blocker administration. The reported duration of the intervention ranged from 3-14 days. F-URS was performed in five studies, while a Kaler study reported tamsulosin use before the PNL procedure. The UAS measures used for each procedure were 9.5/11.5 Fr, 11/13 Fr, 11/14/16 Fr, and 12/14 Fr. A total of four studies reported the outcome of successful UAS insertion, while the incidence of ureteral wall trauma was reported in three studies.

**Risk of bias assessment**

For bias, RCT study design was evaluated using the Cochrane RoB 2.0 risk assessment tool. Overall, the three studies showed good quality regarding the randomization process, intervention, data completeness and outcome measurement, and reported research results. The risk domains of bias evaluated in each study are summarized in Figure 2.

The Newcastle-Ottawa Scale (NOS) instrument was applied to studies with non-randomized designs or observational studies. Aspects evaluated based on this scoring system consist of selection, comparison, and exposure. The total sum of each assessment element ranges from 0-3, indicating the study is of low quality, a score of 4-5 is of moderate quality, and a score of 7-9 is a high-quality study. The assessment results showed that the retrospective studies included in this study had a mean total score of 7, indicating that the included studies were regarded as good-quality studies.

**Meta-analysis result on UAS placement**

There was a significant difference in the success rate of UAS placement in the advantage of the alpha-blocker group compared to the control group with an OR

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**Table 3.** Newcastle-Ottawa Scale as quality assessment tool.

<table>
<thead>
<tr>
<th>No</th>
<th>Author</th>
<th>Year</th>
<th>Study Design</th>
<th>Quality score</th>
<th>Selection</th>
<th>Comparison</th>
<th>Exposure</th>
<th>Total</th>
</tr>
</thead>
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<td>1</td>
<td>Biebel et al.</td>
<td>2020</td>
<td>Retrospective</td>
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<td>2</td>
<td>2</td>
<td>7</td>
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<tr>
<td>2</td>
<td>Erturhan et al.</td>
<td>2019</td>
<td>Retrospective</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>8</td>
<td></td>
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<tr>
<td>3</td>
<td>Kaler et al.</td>
<td>2018</td>
<td>Retrospective</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Figure 2.** Cochrane RoB 2.0 as bias assessment tool.

**Figure 3.** The success rate on UAS placement.

**Figure 4.** Ureteral wall trauma incidence.
of 3.83 (1.83 - 8.00; 95% CI; p = 0.0004). The heterogeneity analysis between studies resulted in an I² index of 0%. Accordingly, the fixed effect model was applied based on the heterogeneity of pooled studies. The success rate analysis on UAS placement is shown as a forest plot in Figure 3.

**Meta-analysis result on ureteral wall trauma incidence**

The meta-analysis results showed a significant difference in ureteral wall trauma, which was higher in the control group than in the alpha-blocker intervention group with OR 0.38 (0.17 - 0.84; 95% CI; p = 0.02 ). Heterogeneity between studies was highlighted by an I² index of 46%, regarded as not significant. The meta-analysis used a fixed effect model based on the heterogeneity of pooled studies. The ureteral wall trauma incidence analysis is shown as a forest plot in Figure 4.

**Association between UAS size and success rate of UAS insertion**

The association between UAS size and the success rate of UAS insertion is illustrated in Figure 5. The difference between the alpha-blocker-administered group and the control group was most substantial (47%) in the study of Kaler et al. which utilized 11/14/16 Fr UAS size. The difference is also seen in the study of Ertuhan et al. with the use of 9.15/14 Fr UAS size (21%). On the other hand, the 12/14 UAS in the study of Biebel et al. had the slightest difference in success rate (2%), but it should be noted that their overall success rate was the highest among the included studies. The graph in Figure 5 shows no clear correlation between the size of the UAS and the improvement of success rate of UAS insertion.

**DISCUSSION**

In this review, we have obtained studies evaluating the effects of alpha-blockers on UAS placement in retrograde intrarenal surgery (RIRS) and percutaneous nephrolithotomy (PCNL) procedures. Available sheaths are produced by various companies with different diameters ranging between 9 to 14 Fr. Current literature suggests that flexible ureteroscopy (FURS) offers an excellent stone-free rate, thus it is becoming an excellent option as the endourological procedure of choice for kidney and ureteral stone management. It also has a higher tolerability profile compared to other alternative procedures. A previous study examined the pre-ureteroscopic use of alpha-blockers. They discovered that there is a significant difference in both safety and efficacy of preoperative alpha-blocker use in ureteroscopy.

An RCT by Koo et al. gives the experimental group alpha-blocker preoperatively. The alpha-blocker group received the same standard treatment in addition to tamsulosin 0.4 mg daily seven days before surgery. Preoperative alpha-blocker and slow sheath placement may reduce maximal ureteral access sheath insertion force. This study showed that preoperative alpha-blocker and slow sheath placement reduced maximal ureteral access sheath insertion force.

Another study also reported its benefit in semi-rigid ureteroscopy for proximal ureteral stones. Current literature also suggests the possibility of utilizing pre-stenting to facilitate UAS placements. Even though stents may reduce the likelihood of active dilation and the risk of ureteral injury, they are associated with adverse symptoms, such as flank pain and dysuria. Pre-stenting also requires a secondary procedure. Active balloon dilation is also an option, however there are risks of ureteral edema and stricture. Therefore, a passive dilation with preoperative alpha-blocker administration seemed to be the best choice as of the conduct of this review. Based on our analysis, the success rate of UAS placement is higher in the alpha-blocker group compared to the control group with an OR of 3.83 (1.83 - 8.00; 95% CI; P = 0.0004). The alpha-1 adrenergic receptor is the most common adrenoreceptor in the prostate and bladder neck tissue. A three-dimensional characterization of the organ has shown that the distal ureter contains the highest density of autonomic nerves. Inhibiting the receptor leads to muscle wall relaxation, decrease in spasm, this facilitating ureteral dilation while decreasing intramural ureteral resistance. In this included studies, the alpha-blockers that were used were 0.4 mg tamsulosin and 8 mg silodosin for 3 to 14 days. The long duration of administration was due to the half-life of the alpha-blockers for at least 5 days to reach a stable dose. Silodosin is believed to reduce postoperative pain, ureteral contraction force, and ureteral peristalsis frequency, thus allowing the ureter to act like a dynamic tube. The passage of UAS in the intramural area of ureter is believed to be the most crucial due to its narrow width. A lot of urologists have stated concern regarding UAS placement failure. Based on these findings, it is unsurprising that several reviews and trials have shown that tamsulosin helps the passage of instruments as well as distal ureteral stones.
especially among 5–10 mm stones.\textsuperscript{34,35} One study in the included studies evaluated alpha-blockers on UAS placement in PCNL. In the study, there is doubling of the rate of successful passage of 16 fr UAS of the group receiving tamsulosin (87\%) compared to no tamsulosin (43\%).\textsuperscript{32} UAS insertion could cause a severe shear force, resulting in ureteral wall injury ranging from erosion to an avulsion.\textsuperscript{46} The friction between the mucosa and the sheath stimulates the nociceptors and may cause acute inflammation leading to pain.\textsuperscript{47} Our analysis showed a significant difference in ureteral wall trauma, which was higher in the control group than in the alpha-blocker intervention group with OR 0.38 (0.17 - 0.84; 95\% CI; \(p = 0.02\)). Even though a subgroup analysis for each subtype could not be performed, silodosin may be more potent for ureteral dilation compared to other subtypes. In the ureter, all subtypes of adrenoceptors can be found. The \(\alpha_1\)A receptors play the main role in ureteral contraction. The \(\alpha_1\)D receptors are mainly found in the intracellular compartment, whereas the smooth muscle cell membranes mainly express \(\alpha_1\)A receptors.\textsuperscript{38,39} Thus, silodosin which is more selective to the \(\alpha_1\)A receptors compared to other subtypes could be more potent for facilitating UAS insertion.\textsuperscript{40} It also has a shorter acting time than other agents. Symptoms generally improve from the day after silodosin administration as opposed to tamsulosin which generates improvements in at least four days to one week.\textsuperscript{41} However, a direct comparison between tamsulosin and silodosin has never been performed. Another factor to consider in this review's findings is the difference in sheath sizes in the study. The difference was most substantial (47\%) in the study by Kaler et al. which utilized 11/14/16 Fr UAS size.\textsuperscript{34,35} The study by Erturhan et al. also showed a major difference with 9.15/914 Fr UAS size (21\%). The additional tamsulosin (0.4 mg/day) was prescribed to the study group (n=25) 2 weeks before the operation.\textsuperscript{42} However, an analysis of the size differences could not be performed in this review.

There are several limitations in this review. Due to the limited number of available studies evaluating UAS, the analysis included both randomized and non-randomized studies. In the studies, the agents used consisted of both tamsulosin and silodosin with various sheath sizes. After new trials are published, a separate analysis for alpha-blocker subtypes and sheath sizes should be performed. There was also one study that used a different classification for defining the degree of ureteral wall injury, which may affect the end results slightly as the parameters were similar. Nevertheless, the currently available data shows a potential benefit in alpha-blockers for UAS insertion. A similar study should be conducted in the future, including studies with a multicenter clinical trial design and a larger sample size.

CONCLUSION
Preoperative use of alpha-blockers, such as tamsulosin and silodosin may increase the success rate of UAS insertion while decreasing the risk of ureteral wall injury in intrarenal endoscopic procedures. Future studies and reviews should consider the variety of alpha-blocker subtypes and sheath sizes to determine the most ideal preoperative preparation for UAS insertion.

CONFLICTS OF INTEREST
The authors declare that they have no conflict of interest.

FUNDING SOURCE
None.

ETHICS COMMITTEE APPROVAL
This systematic review and meta-analysis do not require ethical approval.

AUTHOR CONTRIBUTION
- Muhlis Yusuf (M.Y.) is involved in the concept and project design, materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.
- Niwanda Yogiswara (N.Y.) is involved in the materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.
- Mohammad Rifki Setiawan (M.R.S.) is involved in the materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.
- Sirin Salsabila (S.S.) is involved in the materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.
- Mohammad Ayodhia Soebadi (M.A.S.) is involved in the concept and project design, supervision, resources, materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.
- Soetojo Wirjopranoto (S.W.) is involved in the concept and project design, supervision, resources, materials, literature search, data collection and/or processing, analysis and/or interpretation, writing the manuscript, and final approval of the version to be submitted.

REGISTRATION OF RESEARCH STUDY
- Name of the registry: PROSPERO
- Unique Identifying number or registration ID: CRD42022342811
- Hyperlink to registration: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=342811

REFERENCES


