The Efficacy of Preoperative Tamsulosin on Ureteroscopy Access in Pediatrics: A Systematic Review and Meta-Analysis

Nicholas Andrian Singgih, M.D.*, Jacinda Risha Oktaviani, M.D.*, Raden Honggo Pranowo Sampurno Secodiningrat, M.D.*, William Adipurnama, M.D.*, Egi Edward Manuputty, M.D.*, Kevin Tandarto, M.D.**

**Department of Urology, Primaya Hospital PGI Cikini, Jakarta, Indonesia. **Faculty of Medicine and Health Science, Atma Jaya Catholic University of Indonesia, Jakarta, Indonesia.*

ABSTRACT

Objective: The incidence of urolithiasis in pediatrics increases to 4-10% annually. One of the methods for treating urolithiasis is ureteroscopy (URS). The small anatomy in pediatrics often makes the initial URS unsuccessful. Alpha blockers, a drug that can relax the ureteral muscles, is a therapy that can be considered before URS is carried out. The objective of this study is to evaluate the efficacy of preoperative tamsulosin for URS access in pediatrics.

Materials and Methods: We conducted a search using four databases, including PubMed, EBSCO, Cochrane Library, and ProQuest. This study includes randomized controlled trials (RCTs), retrospective and prospective studies, which compared the efficacy of preoperative alpha blockers and placebo or non-placebo controls in pediatrics undergoing ureteroscopy. The outcome of interest was the success rate of URS access and the duration of surgery.

Results: A total of 120 studies were identified from a database search. There were 3 studies included in this review involving 235 patients. The meta-analysis was conducted using a random-effects model. The results of the meta-analysis showed that alpha blockers provided a successful rate of ureteroscopy access in pediatric patients (Odds ratio (OR) 2.73; 95% confidence interval (CI) 1.52 up to 4.91; p=0.0008). Duration of surgery did not show significant results (Mean difference (MD) 3.46; 95% CI -3.59 up to 10.50; p=0.34).

Conclusion: Preoperative administration of tamsulosin may increase the success rate of ureteroscopy access in pediatric patients.

Keywords: Alpha blockers; pediatric; systematic review; tamsulosin; ureteroscopy (Siriraj Med J 2023; 75: 655-664)

INTRODUCTION

The incidence of urolithiasis in children within the past twenty years continues to increase steadily every year with a ratio of 4-10% per year.[1] In children it will be difficult to determine the pain experienced, but the symptoms typically in the form of crying, anxiety, vomiting, hematuria, traces of blood or small stones on diapers, or recurrent urinary tract infections (UTI) with painful micturition.[2] 20% of kidney stones are found in the ureters which cause discomfort and can result in kidney damage.[3] The modality of treatment that can be given is influenced by the location and size of the stone, degree of back-pressure, as well as associated UTI.[4] The treatment is in the form of observation, medical expulsive therapy (MET), ureteroscopy (URS), and ureterolithotomy.[3] The AUA and the Endourological Society recommend URS and ESWL for patients who have failed MET and may require surgical intervention. URS has been evaluated

Corresponding author: Nicholas Andrian Singgih
E-mail: nicholasandrian1606@gmail.com
Received 30 June 2023 Revised 24 July 2023 Accepted 25 July 2023
ORCID ID:http://orcid.org/0000-0002-7331-3070
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as safe for both adults and children, although there is a risk of failure in the initial attempt.[1] However, failure rates are higher in children than in adults due to the smaller width of the ureter, making URS challenging in children.[1,3]

There is controversy regarding the risk of routine prestenting and dilation of balloons to gain ureteral access in children because of the risk of ureteral perforation and ureteral stricture. Ureteral access is often obstructed at the ureteral orifice or intramural ureter, where there are many α1-adrenergic receptors. The presence of alpha blockers can reduce muscle contractions around the ureteral orifice.[5] In addition, it can reduce basal tonicity, reduce peristaltic activity and intraluminal tone.[3] To our knowledge, there is not much literature about the use of tamsulosin for ureteroscopy in pediatrics. Thus, we conduct a systematic review and meta-analysis to find out the effectiveness of tamsulosin for ureteroscopy access in pediatrics.

MATERIALS AND METHODS

Data sources and literature search strategy

We conducted a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines 2020.[6] Our search encompassed relevant literature from PubMed, Proquest, EBSCO, and the Cochrane Library databases. We utilized specific search terms such as "alpha blocker", "alpha adrenergic blocker", "tamsulosin", "silodosin", and "α-blocker" in conjunction with terms like "ureteroscopy", "ureteroscopic", and "retrograde intrarenal surgery". Furthermore, we included terms related to the target population, such as "children", "adolescence", "pediatric", and "school-age children". To ensure comprehensiveness, we manually examined the reference lists of selected manuscripts for potential articles that met our inclusion criteria.

Eligibility criteria

This systematic review incorporated a variety of study designs, including Randomized Control Trials (RCTs), case-control studies, retrospective cohorts, and prospective cohorts. To be included in this review, studies needed to fulfil specific criteria. Firstly, studies had to compare the use of perioperative alpha blockers with no alpha blockers in the context of ureteroscopy (URS) access. This comparison aimed to examine the potential effects of alpha blockers on the outcomes of interest. Secondly, the study population had to consist of patients who were under the age of 18. Lastly, the reported outcomes of interest included URS success in the initial attempt and surgical time. Those outcomes were chosen to assess the efficacy and efficiency of utilizing perioperative alpha blockers during URS procedures. To maintain the rigor of our review, we excluded certain types of articles that did not meet our criteria, including case reports, reviews, and conference abstracts, as they were not deemed suitable for inclusion in our analysis.

Data extraction

The data extraction process was carried out independently by 3 reviewers. The data extracted included first author, year of publication, country where the study was conducted, study design, sample sizes, age, sex, body mass index (BMI), stone size, duration of alpha blocker administration, surgical time, and success rate. The primary outcome was the success rate in the initial URS attempt. Secondary outcome was the length of surgical time. Disagreements or discrepancies were discussed by all authors.

Methodological quality and risk of bias assessment

Six reviewers contributed to assessing the quality of bias, with each study independently evaluated by two reviewers using the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies. The NOS is a commonly used tool to assess the quality of non-randomized studies. The maximum score on the NOS is 9. Studies that received a score of 7-9 stars were considered to have a low risk of bias, studies scoring 4-6 stars were considered to have moderate risk, while studies scoring 3 or less stars were considered to have a high risk of bias.[7] This rigorous assessment process ensured a comprehensive evaluation of the included studies and provided valuable insights into their methodological quality and potential sources of bias.

Statistical analysis

For the analysis of primary outcomes with dichotomous data, we utilized an OR along with a 95% CI. A p-value below 0.05 was considered statistically significant. This approach allowed us to assess the association between the use of preoperative alpha blockers and the outcomes of interest in a binary manner. On the other hand, secondary outcomes, which involved continuous variables, were analyzed using weighted mean differences (WMD). This method enabled us to compare the differences in means between groups and quantify the effect sizes for these variables. To assess heterogeneity between studies, we calculated the I^2 index. If the I^2 value exceeded 50%, indicating substantial heterogeneity, we applied the random effects model for the meta-analysis. Conversely, if

the I^2 value was below 50%, indicating low heterogeneity, we employed the random-effect model. These models help account for differences across studies and provide a pooled estimate of the effect size. For the statistical analysis, we used RevMan 5.4. software on a Macbook platform. This widely used software facilitated the analysis and synthesis of the data, allowing us to generate forest plots and descriptive narratives to present the outcomes visually and concisely.

RESULTS

Literature search

The comprehensive flow diagram of study selection with subsequent exclusions is presented in Fig 1. A total of 120 studies were found using the search term in four databases. From the first screening, we excluded 42 articles because they did not meet our inclusion criteria from the screening of the title and the abstract. We included 3 suitable English publications in the meta-analysis after removing duplicates and examining the titles, abstracts, and full texts. Of these studies, two were published from the USA and one from Pakistan.

Result of literature extraction

Study characteristic

The baseline characteristics of the included studies are presented in Table 1. This study consisted of three articles, including two cohort studies and one case-control study, with a total of 235 participants.[1,3,5] The average age in each group ranged from 11.7 to 13.7 years old. The intervention groups received alpha blockers (specifically, tamsulosin), while the control groups did not receive alpha blockers. The duration of alpha blocker administration before the ureteroscopy procedure ranged from 2 to 7 days. All studies utilized tamsulosin as the alpha blocker intervention. The average body mass index

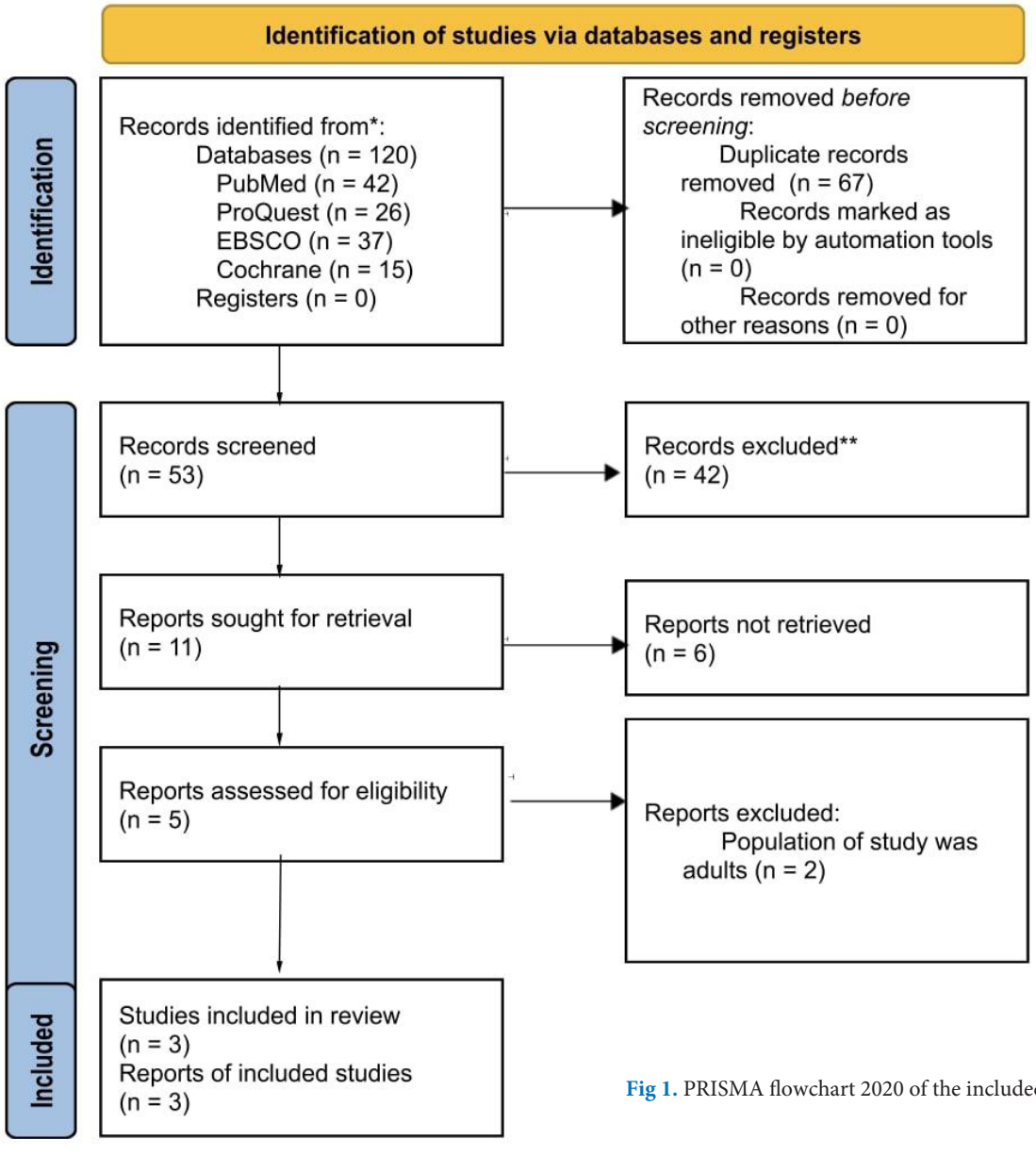

Fig 1. PRISMA flowchart 2020 of the included studies.

TABLE 1. Characteristics of included studies.

Author, year	Country	Study design	Group	Protocol	Duration of administration	Uretroscope	Age (year)	Body mass index (BMI)	Stone size (mm)	Length of surgery (min (SD))	Outcome	Success rate (%)	Stone free rate (%)
McGee LM, et al., 2021.[1]	USA	Retrospective	Intervention	Tamsulosin 0.4 mg	>=7 days	Olympus P6 Flexible URS	13.0	23.3	6.5	40.5 (26.2)	Success rate, stone free rate	62%	75%
			Control	No tamsulosin			13.7	23.2	6. 3	36.1 (16.0)	Success rate, stone free rate	39%	50%
Morley C, et al., 2020.[5]	USA	Retrospective	Intervention	Tamsulosin 0.4 mg	2 days	Semi rigid (wolf 4.5 Fr),	12.2	23.8	2	NA	Success rate	88%	NA
			Control	No tamsulosin		flexible URS (Storz 7.5 Fr)	11.7	21.2	3.25	NA	Success rate	65.40%	NA
Khan A, et al., 2022.[3]	Pakistan	Case control	Intervention	Tamsulosin 0.4 mg	7 days	NA	12.9	24.1	6.59	43.91 (20.11)	Success rate	72.73%	NA
			Control	No tamsulosin			12.9	25.2	7.44	40.70 (22.37)	Success rate	52.73%	NA

(BMI) ranged between 21.2 and 25.2. The average stone size, as reported in the studies, ranged between 2 and 7.44 mm. Based on the length of surgery, the administration of alpha blockers took longer compared to the absence of alpha blockers. The success rate of the three studies indicated that the administration of alpha blockers led to an increased success rate of ureteroscopy access in pediatric patients. There were significant differences of patients' age, stone and URS size between the two cohort studies.[1,5]

Quality assessment

Quality assessment was conducted to evaluate the risk of bias using the Newcastle-Ottawa Scale (NOS). The results revealed that the two retrospective studies included in this study obtained a mean total score of 7, while the case-control study obtained a mean total score of 7 as well. These scores indicate that the included studies were considered to be of good quality. The NOS is a widely recognized tool for assessing the quality of non-randomized studies, and its application in this study provides confidence in the reliability and validity of the findings. The high scores obtained by the included studies suggest that they had a low risk of bias and were methodologically robust.[7] The NOS assessment is presented in Table 2.

Meta analysis result on the success rate of ureteroscopy access

There was a significant difference in the success rate of ureteroscopy access between the alpha blockers group and the control group, with an odds ratio (OR) of 2.73 (1.52-4.91; 95% confidence interval; p=0.0008). Heterogeneity analysis among the studies yielded an I2 index of 0%. Therefore, a random-effects model was applied based on the collected study heterogeneity. The analysis of the success rate of ureteroscopy access was presented as a forest plot in Fig 2. This funnel plot showed that it is symmetrical, indicating a low risk of bias (Fig 3).

Meta analysis result on length of surgery

Among the 3 studies included, only 2 studies were measuring the length of surgery. Between the control group and the alpha blocker group, there was no significant difference in surgical time during the ureteroscopy surgery, with a mean difference of 3.46 (-3.59-10.50; 95% confidence interval; p=0.34). The heterogeneity analysis among the studies was low (P=0.79, I^2=0%), and a random effect model was used for data synthesis. The analysis of length surgery was presented as a forest plot in Fig 3. This funnel plot showed that it is symmetrical, indicating a low risk of bias (Fig 5).

DISCUSSION

Urolithiasis is a common case, even in children. Recently, several studies have reported an increase in the incidence of pediatric urolithiasis.[1,4,5] McGee LM, *et al.* described the incidence in the last 20 years has been estimated at 4-10%. The increasing incidence of urolithiasis in children has strengthened the evaluation of kidney stone management.[1] Pediatrics need a precise identification of the underlying cause and personalized treatments to prevent recurrences of stone formation. It is crucial to see the medical history, find out urinary and dietary habits, perform some tests such as urine and blood tests, as well as analyze urinary stone composition.[8] Disease recurrence can be prevented by dietary adjustment and pharmaceutical intervention. Acute management of the condition comprises monitoring with supportive care, medical expulsive therapy (MET), and surgical intervention.[9] In the past, treatment for urinary tract stone diseases was performed by open surgeries, but recently there has been a significant drive toward minimally invasive surgery (MIS), such as extracorporeal shockwave lithotripsy (ESWL), ureteroscopy (URS), retrograde intrarenal surgery (RIRS),

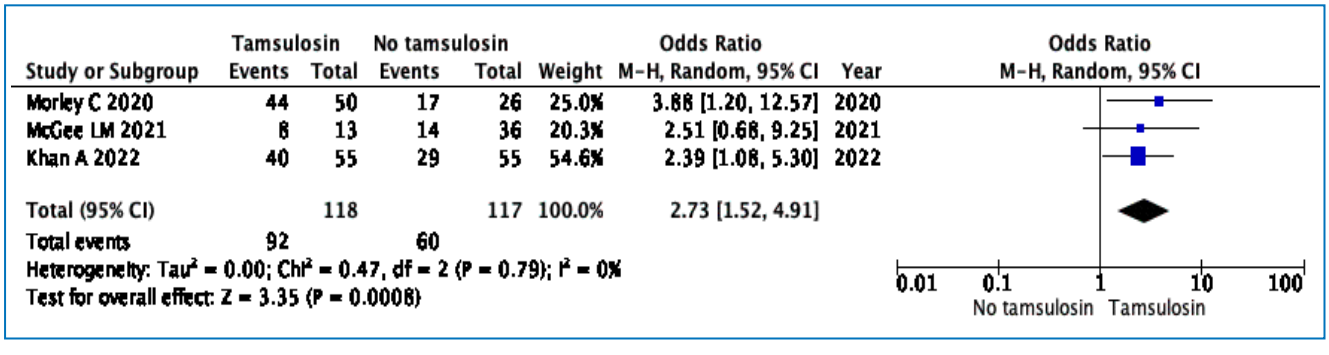

Fig 2. The success rate of ureteroscopy access. CI = Confidence Interval

TABLE 2. Newcastle Ottawa Scale for cohort.

No	Author, year	Selection				Comparability	Outcome			Total score
		Representative of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstrain that outcome of interest was not present at start of study	Comparability of cohort on the basis of the design or analysis	Assessment of outcome	Was follow up long enough for outcome to occur	Adequacy of follow up cohort	
1	Morley, et al. (2020)	1	1	1	1	1	1	0	1	7
2	McGee et al. (2021)	1	1	1	1	1	1	0	1	7

TABLE 3. Newcastle Ottawa Scale for case control.

No	Author, year	Selection				Comparability	Outcome			Total score
		Is the case definition adequate	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls on the basis of the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	
1	Khan et al. (2022)	0	1	1	1	1	1	1	1	7

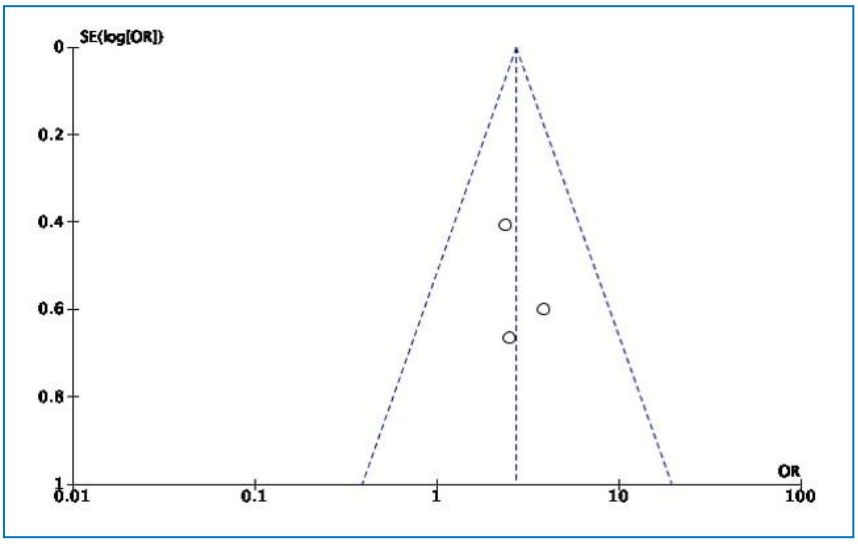

Fig 3. Funnel plot of success rate ureteroscopy access for publication bias. OR = Odds Ratio

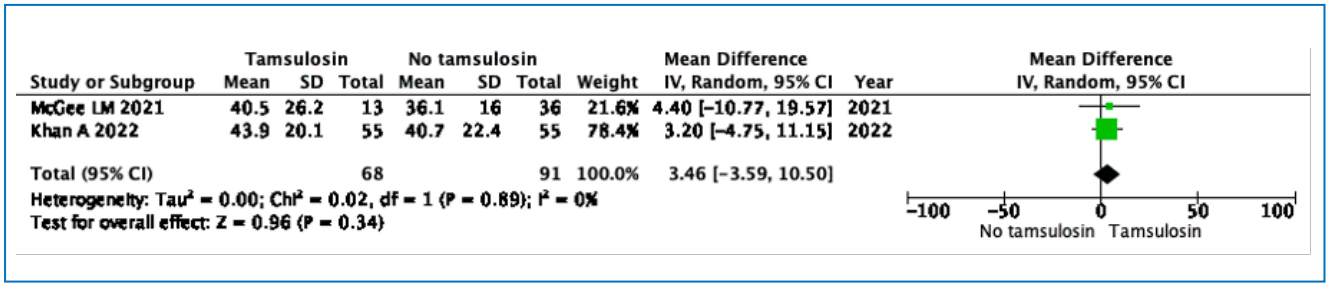

Fig 4. The surgical time during ureteroscopy procedures. CI = Confidence Interval

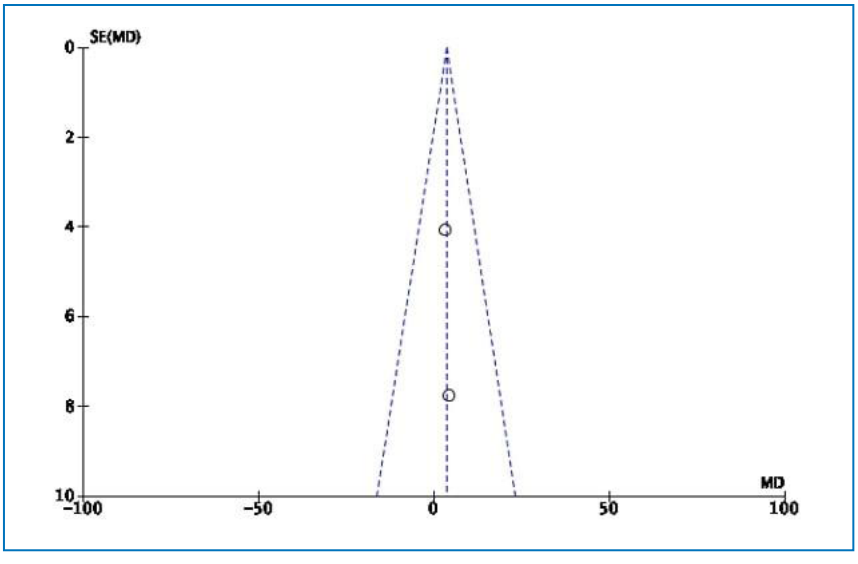

Fig 5. Funnel plot of surgical time during ureteroscopy procedures. MD = Mean Difference

and percutaneous nephrolithotomy (PCNL). According to the European Association of Urology (EAU) guidelines for the management of urinary stone disease in children, robotic-assisted laparoscopic surgery approaches are good alternatives in patients with a history of previous failed endoscopic procedures, complex renal anatomy (ectopic or retrorenal colon), concomitant ureteropelvic junction obstruction (UPJO) or calyceal diverticula, mega-ureter, or large impacted stones. Miniaturized instruments and new technological developments have led to many innovations in the surgical management of pediatric urolithiasis.[8]

The use of ureteroscopy for stone management in children can be a good option. Straub, *et al.* mentioned that the URS procedure is the most ideal procedure for stones in the mid and distal ureters.[9] In a study conducted by Whatley A, *et al.*, with an average age of 8.5 years showed that the use of ureteroscopy in the

treatment of urolithiasis resulted in an 87% stone-free rate with an average operating time of 62 minutes.[11] Another research according to Nerli, *et al*. found that the use of ureteroscopy as therapy in children under 60 months of age proved effective and safe in ureteral and renal pelvic stones. However, in this study, before the ureteroscopy procedure, dilatation of the ureter was required first.[12] It is challenging and risky to advance a ureteroscope into the non-dilated ureter; failure to do might result in the procedure's failure.[13] A systematic review by Rob S, *et al*. showed equally high SFRs and safety profiles of URS in pediatrics may be attained by medium-volume centers as well as large-volume centers, hence encouraging expanded URS use in facilities that do fewer operations annually.[14]

According to meta analysis from Ziaeefar, using medical compulsive therapy (MET) enhances stone expulsive rate while decreasing stone expulsive time.[15] The use of alpha-blockers such as tamsulosin is generally used for medical compulsive treatment (MET) of distal ureteral stones in adults and children.[1] Alpha-1 adrenergic receptors are the most common adrenoceptors in prostate and bladder neck tissue. The drug also has the ability to relax, dilate the intramural distal ureter, and is predicted to be able to lower ureteral peristalsis and intraluminal pressure due to the presence of alpha-1 receptors in the distal ureter. Alpha-1 adrenergic receptors are the most common adrenoceptors in the urinary tract, including the ureters.[16] In the ureters, alpha-1 adrenergic receptors are distributed more distally than in the middle and proximal portions, especially the α1D subtype.[17] Stimulation of α receptors increases the strength of ureteric contractions and the frequency of ureteral peristalsis. Meanwhile, the mechanism of α-antagonists includes reducing ureteral spasm, increasing proximal stone pressure, relaxing the ureter in the distal area, and reducing the tone and frequency of contractions.[18-20] Due to the relaxing effect of distal ureteral tone, the preoperative use of tamsulosin may increase the successful insertion of ureteral access in children.[5]

A meta-analysis was prepared by Alshaikhan A, *et al*. on the use of pre-ureteroscopy alpha-blockers. In this study, it was concluded that the use of preoperative alpha blockers provides a high success rate of ureteroscopic access and reduces the need for ureteral dilation. In this study, there was no age limit between children and adults.[21] Another study by Ahmed AF, *et al*. who studied the use of adjunctive tamsulosin therapy before ureteroscopy procedures in adult patients, showed that tamsulosin decreased the failure rate of ureteroscopic access, shortened the duration of surgery, and reduced the rate of complications.[22] A pooled analysis by Tan H, *et al*. described false lumen development, perforation, and mucosal hemorrhage as complications that may result from ureteroscopy. When compared to the placebo group, the adjunctive alpha-blocker medication was linked to a considerably reduced risk of all these complications.[13] A meta analysis by Sesari SS, *et al*. showed that administration of adjunctive alpha blocker also minimizes colic episodes.[23] In children, the lumens of the ureters are narrow, making ureteroscopy has many failures compared to adults, thus providing a more complex challenge.[1,3]

In the present systematic review and meta analysis study, we attempted to provide a comprehensive summary of the evidence available to assess the use of alpha blocker on the success of ureteroscopy access in pediatrics. The findings of this study may have important implications for the management of urolithiasis in pediatrics and may guide clinical decision-making regarding the use of alpha blocker preoperative in this population. In our included studies, the alpha blocker used was all tamsulosin. The studies compared patient outcomes who received tamsulosin preoperative and those who did not. There were two outcomes analyzed, the success of the initial URS attempt and the surgery length.

The meta-analysis was conducted on 3 studies involving 235 participants, comparing preoperative administration of alpha-blockers with no use of alpha-blockers showing that preoperative administration of alpha-blockers increased the success rate of ureteroscopic access. In these studies, the alpha blocker used was tamsulosin 0.4 mg with an average dose of 2-7 days before the URS procedure because tamsulosin was found to have a rapid onset of action after 8 hours when used for benign prostatic hyperplasia.[3,5] Meanwhile, another research stated that administration of alpha-blockers takes at least 5 days to achieve a stable dose.[16] Tamsulosin, a highly selective 1d adrenoceptor antagonist, has been shown to boost stone ejection rates for distal ureteral calculi in several studies.[24] Side effects that arise as a result of the administration of tamsulosin in children can occur in the form of hypotension, asthenia, syncope, palpitations, somnolence, nausea, vomiting, headache, nasal congestion, and dizziness. Sun K, *et al* stated the side effects of alpha blockers were 2.3 times higher than placebo. According to further subgroup analysis, the use of tamsulosin was positively connected with adverse drug reactions (ADRs) in children with ureteral calculi, but doxazosin and silodosin had no statistically significant impact on the likelihood of treatment-emergent adverse events (TEAEs).[25]

Meta-analysis conducted in 2 studies showed

that preoperative administration of alpha blockers did not have a significant effect on the duration of surgery compared to without alpha blockers. Research by Demir M, *et al.* demonstrated that preoperative administration of tamsulosin in patients over 18 years of age resulted in a shorter operating time than those who did not receive tamsulosin.[26] Other studies in populations under 18 years stated that the administration of tamsulosin before surgery did not provide significant results.[1,3] The factors that can affect the duration of surgery in ureteroscopy procedures can vary. Some factors that can influence the surgery duration include stone complexity, stone size, patient's anatomical condition, surgeon's experience, techniques used, and available equipment. A retrospective study by Whitehurst L, *et al.* showed that operative times are longer while treating large, multiple stones.[27] Another retrospective study by Katafigiotis I, *et al.* described that total stones volume, type of ureteroscope used, stone number, main surgeon experience, radio-opacity on KUB X-ray, nurse's experience, operating room type, and having a nephrostomy tube prior to surgery were several important preoperative predicting factors that affect total operative time.[28] The duration of ureteroscopy surgery can be influenced by the complexity of the stone being treated. Stones with high complexity, such as larger size or additional complications like infection or obstruction, may require a longer operating time. Additionally, stone size can also affect the surgery duration. Larger stones typically require more time to be fragmented or removed.[29] A single center analysis by Ito H, *et al.* resulted larger stone volume, a surgeon with less expertise, higher HUs, and a lack of preoperative stenting were all shown to extend the length of the flexible URS procedure in general and the period after fragmentation begins in particular. However, it was more challenging to estimate the amount of time that would be needed to locate the stone via ureteroscopy and place the access sheath before beginning fragmentation.[30] The patient's anatomical condition can also impact the surgery duration. If the patient has anatomical abnormalities or challenging structures to access, the ureteroscopy procedure may take longer.[31,32] Experienced surgeons may be more skilled in performing the procedure quickly and efficiently, thereby reducing the operating time.[33-36]

There are several limitations to this systematic review and meta analysis study. First, the number of studies on preoperative alpha blockers in children were small. Second, the study design was non-RCT. Third, this study only provides one type of alpha blocker, namely tamsulosin, therefore cannot analyze the effects of other alpha blockers. Fourth, the duration of administration of alpha blockers was varied, giving rise to the potential of bias. Fifth, studies were done in only two countries which may not be representative of the general population of urolithiasis in pediatrics. Our suggestions for further research are to conduct research with a large study population with RCT study design along with preoperative alpha blockers other than tamsulosin such as silodosin and doxazosin. In addition, we suggest outcomes such as side effects, and postoperative pain reduction effects of alpha blockers in the pediatric population. Lastly, further study suggested using URS with a smaller size.

CONCLUSION

Preoperative administration of tamsulosin increases the success of ureteroscopy access in pediatrics. For the length of surgery, there was no significant difference between the use of tamsulosin as an alpha blocker with the control group.

Ethical approval

This research did not involve human subjects; therefore, it was exempt from ethical clearance

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No funding

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