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Safety and effectiveness of α-adrenergic blockers for pediatric urolithiasis in the distal Ureter: A systematic review

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Abstract

Medical expulsive therapy is now widely accepted by parents, and pediatric urolithiasis is a common condition. We searched PubMed, Embase, and the Cochrane Library databases for pertinent publications. We considered all published randomized controlled trials (RCTs) on the treatment of pediatric distal urolithiasis with α-adrenergic blockers or placebo. The results included information on stone ejection rate, stone expulsion time, pain episodes, analgesic use, adverse events, and related subgroup analyses. Our findings suggest that well-tolerated α-adrenergic blockers can successfully cure juvenile distal urolithiasis. We also discovered that silodosin is the most effective pharmaceutical approach, with a greater percentage of ejection.

Keywords: Urolithiasis; α-adrenergic blockers; Distal ureteric stone; Stone expulsion; Medical expulsive therapy

1. Introduction

Incident of pediatric urolithiasis has been reportedly increasing, with an estimated prevalence of 0.1-5% [1]. Urinary stones in children can occur due to various factors, considering metabolic, environmental, and dietary aspects [2]. Urolithiasis commonly causes hematuria, dysuria, and pain in older children, whereas younger children may experience non-specific symptoms such as irritability [1]. Treatment for urolithiasis depends on stone size, location, composition, and urinary system anatomy[3]. Endoscopic technology has led to a shift from open stone surgery to less invasive techniques [4,5]. Medical expulsive therapy (MET) is recommended for minor distal ureteric stones to prevent anesthesia and associated expenditures. α-adrenergic blockers are the chosen medicine in this setting [2]. In recent years, α-adrenergic blockers have been recommended for the treatment of distal Ureter stones [3,6]. Research indicates that α-adrenergic blockers effectively improve both the rate and duration of spontaneous stone ejection [7]. Although α-adrenergic blockers have been used to treat urolithiasis in children as MET, there is limited information on their effectiveness [8]. This systematic review, utilizing data from published randomized control trials, evaluated the effectiveness of α-adrenergic blockers as a treatment for distal ureteral stones in pediatric patients.

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2. Methodology

2.1. Protocol

This is a systematic review and meta-analysis investigating the effect of alpha-adrenergic agents in the treatment of distal ureteric stones in the pediatric population. Our report follows the PRISMA protocol. (Fig 01)

2.2. Eligibility Criteria

2.2.1. Exclusion criteria

Studies with no comparison between α-adrenergic blockers and cases.

2.2.2. Poor randomization

No documentation of adverse events and/or duration of stone expulsion

2.3. Inclusion Criteria

Studies have reported adverse events, stone expulsion time, and stone size after using α-adrenergic blockers on distal ureteric stones in the pediatric population.

2.4. Search Strategy

A methodical search was conducted using multiple databases of research-based literature including Pub-Med, Cochrane, Google Scholar, EMBASE and Web of Sciences from 2000 – 2024. We have limited our search to pediatric subject studies, no language restriction was applied. Table 1 shows a comprehensive search strategy. In each of the aforementioned datasets, we used a search method that involved multiple keyword combinations in the following order.

- "α-adrenergic blockers efficacy in distal ureteric stones of pediatric population" [Title/Abstract]
- B. "Outcomes of α-adrenergic blockers in the pediatric population" [Title/Abstract]
- C. " α-adrenergic blockers and medical expulsive therapy agent in children" [Title/Abstract]
- D. [A] AND [B] AND [C]

2.5. Study selection

The investigator retrieved the most relevant studies based on abstracts and titles. After reviewing the complete articles, the most pertinent ones were chosen in accordance with the eligibility requirements. Tables with the pertinent data were created, saved, and extracted.

2.6. Data Extraction

Two investigators extracted the data from eligible articles, and compression of extracted data was discussed to resolve discrepancies. The remaining investigators reported any remaining differences, and each study was reported in the form of a table along with the complete title, first author, date of publication, purpose/aim of the study, study setting, sample size of study, limitations, and conclusion.

2.7. Statistical Analysis

RevMan and R were used to sort, analyze, and present data graphically. Reported test results of relevant data including chi-square, Multivariate survival analysis, Time-dependent survival analysis, disease-free survival, Hazard ratio, and incidence rates were reported from all included studies.

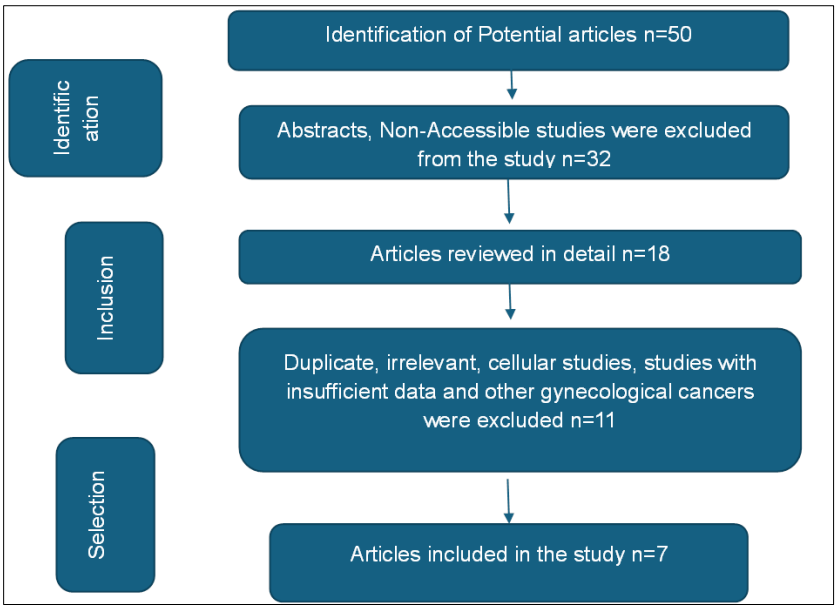

Figure 1 PRISMA flow chart of study selection

3. Results

3.1. Study Characteristics

A total of 7 randomized controlled trials were included in the systematic review, starting from 2000 to 2024, with total sample size of 429, only tamsulosin was used in single study as Medical expulsive therapy (MET) and Silodosin was also used in only one study, while the combination of silodosin and tamsulosin was used in three studies respectively. Remaining studies used Doxazosin. The mean duration of therapy documented in included studies was 3.2 ± 1.2 weeks, while the mean stone size was reported as 11.7 ± 2.3 mm. (Table 01)

Table 1 Characteristics of included studies in review

Year	Study design	Control	Cases	Sample size	Duration of therapy	Dosage	Stone size
(Aydogdu et al. 2009)	RCT	Analgesics	Doxazosin	39	3	0.03 mg/kg/d	≤ 10 mm
(Mokhless et al. 2012)	RCT	Analgesics	Tamsulosin	61	4	0.4 mg/d	≤ 12 mm
(Erturhan et al. 2013)	RCT	Analgesics	Doxazosin	45	3	0.03 mg/kg/d	≤ 10mm
(Aldaqadossi et al. 2015)	RCT	Analgesics	Tamsulosin + Silodosin	61	4	0.4 mg/d + 4mg/d	≤ 10mm
(fahmy et al. 2017)	RCT	Analgesics	Silodosin	60	4	4 mg/d	
(Elgalaly et al. 2017)	RCT	Analgesics	Tamsulosin + Silodosin	37	4	0.4 mg/d + 4 mg/d	≤ 10mm
(Soliman et al. 2021)	RCT	Analgesics	Tamsulosin + Silodosin	126	4	0.4 mg/d + 4 mg/d	≤ 10mm

3.2. Stone expulsion Time

Mean stone expulsion duration of cases and controls were documented and results indicated patients treated with α-adrenergic blockers expelled the stone in less time as compared to controls. The mean difference was -10.3 to -0.2 days with Tamsulosin and silodosin combination versus Doxazosin respectively. While accumulated mean duration of stone expulsion in cases was 9.2 ± 2.1 days while controls reported mean stone expulsion duration of 20.4 ± 4.3 days with a mean difference of 11.2 ± 2.2. (Table 02)

Table 2 Reported duration of stone expulsion in cases compared to controls

Expulsion time reported in studies			
Studies	**Cases**	**Controls**	**Mean diff**
	mean ± SD	**mean ± SD**	
9	7.7 ± 1.9	18 ± 1.73	-10.3
10	5.9 ± 2.1	6.1 ± 2.3	-0.2
11	7 ± 4.3	10.4 ± 4.7	-3.4
12	6 ± 0.37	8 ± 0.37	-2.00
3	8.2 ± 3.4	14.5 ± 4.5	-6.3
13	16.2 ± 4.2	21.2 ± 5.6	-5

3.3. Sub category analysis

Adverse events were reported as episodes of hematuria, nausea, need of analgesic (oral or intramuscular) allergic reactions or need to stop medications and get surgical intervention. Highest number of reported adverse events was from 2021 study with 16 reported incidents; the risk of adverse events with α-adrenergic agents is reportedly higher ranging from 1.38 – 8.81 respectively. (Table 03)

Table 3 Reported adverse events from included studies of review

Adverse events				
Study	**Cases**	**Controls**	**OR**	**95% CI**
9	3	0	7.98	0.40-161.23
10	0	0		
11	3	0	8.81	0.42-183.61
12	1	0	2.74	0.11-71.04
3	9	6	1.38	0.42-4.49
13	16	5	4.18	1.41-12.41

The stone expulsion time was estimated with accordance of stone size, the two categories of stone sizes were< 5 mm and > 5 mm respectively, three studies reporting < 5mm stone size showed a minimum of 2.91 and a maximum of 25.91 OR while the remaining three studies with stone sizes of >5mm reported lower odds of stone expulsion with minimum OR of 1.75 and maximum of 9.14 respectively. (Table 04)

Table 4 Comparison of stone expulsion duration associated with stone size

Stone expulsion time according to stone size					
Stone size	**Study**	**Cases**	**Controls**	**OR**	**CI 95%**
< 5 mm	10	9	8	3.38	0.29-39.32
	12	9	5	25.91	1.23-546.67
	3	16	11	2.91	0.23-36.16
> 5 mm	10	7	6	1.75	0.22-14.22
	12	8	1	9.14	0.90-92.40
	3	13	7	3.71	0.70-19.59

4. Discussion

Pediatric urolithiasis is more common in underdeveloped nations than to industrialized countries [14,15]. Pediatric patients typically require many treatments for urolithiasis due to its high recurrence rate [16–18]. Treatments such as placebo, a-adrenergic blockers (e.g., tamsulosin, silodosin, doxazosin), calcium channel blockers (e.g., nifedipine), and adjuvant treatments (e.g., steroids or tolterodine) are commonly used instead of surgery due to its high cost and procedural risk [4,6]. Analgesics can alleviate pain and promote autonomous stone evacuation, whereas a-adrenergic blockers can limit uncoordinated frequency and sustain propulsive contractions, resulting in faster stone expulsion and less discomfort. The effectiveness of a-adrenergic blockers in treating pediatric urolithiasis in the distal ureter remains unclear [2,5,19].

Our review compared a-adrenergic blockers (tamsulosin, doxazosin, and silodosin) to placebo in treating juvenile urolithiasis with stones less than 12mm. A-adrenergic blockers were found to be effective in treating pediatric urolithiasis in 7 randomized controlled trials including 429 individuals. A-adrenergic blockers improved stone expulsion rates and reduced expulsion time. Additionally, children who received a-adrenergic blockers experienced fewer pain episodes and required fewer analgesics.

We also conducted subgroup analysis based on drug and stone size. Tamsulosin, silodosin, and doxazosin significantly improved expulsion rate, while tamsulosin and silodosin significantly reduced expulsion time. However, doxazosin had no impact when compared to placebo. Tamsulosin and silodosin significantly reduce the frequency of pain episodes. This study confirms that silodosin has a higher expulsion rate, shorter expulsion time, and fewer pain episodes in pediatric patients compared to tamsulosin [1,2,20–22].

Over the last 20 years, advancements in endourologic technology have made it possible for urologists to utilize smaller, more flexible endoscopes with more efficiency [8,23–25]. According to published research adults with stones less than 5 mm have an 80% chance of passing them naturally [26], while a meta-analysis found that stones under 5mm and 5-10mm had 68% and 47% spontaneous passage rates, respectively, during follow-up [1,6,7].

The size and position of ureteral stones significantly impact their ejection rate and interval, according to the statistics,[1,27,28]. However, in our review calculi less than 5 mm had higher expulsion rates with α-adrenergic blockers as compared to analgesics [3,10,12]. In 1998, doxazosin, an α -blocker, was utilized to speed up the natural transit of ureteral calculi, since then, randomized controlled trials have employed α -blockers to treat ureteral stones [10]. These medicines effectively reduce ureteral muscle tone and intramural pressure, leading to faster stone transit, patients on α -blockers and calcium channel blockers had higher spontaneous passing rates compared to those using standard management measures(Sun et al. 2022).

Renal obstructions are known to cause ureteral muscular spasms, submucosal edema, discomfort, and infection [29]. Increased intraluminal pressure activates neurons in the ureter's smooth muscle and mucosa layers, leading to discomfort. Conservative therapy tries to minimize muscle spasms, urethral edema, and infections while lowering discomfort until spontaneous evacuation occurs [30]. Clinicians have employed pharmacological medications including calcium channel blockers and steroids to treat this condition [27]. Management of such symptoms in pediatric population is challenging as the child can only show limited signs apart from symptoms and verbal identification of issues are absent [2,3,10,31].

Some research examines how alpha-blockers and anticholinergics interact. [12] found that while tamsulosin effectively removes ureteral stones, tolteridine does not offer any further benefits. Prospective randomized trials show that using alpha-blockers to treat distal ureteral stones in adults reduces the need for analgesics and improves patient suffering during stone transit.

The MET allows for spontaneous stone passage in DUS occurrence [1,2,32]. Several studies have evaluated the effectiveness and safety of α-adrenergic blockers in adult populations [2019]. There is limited research on the use of α-blockers as MET in pediatric patients [13,33]. Previous trials have demonstrated the safety of these medicines for treating voiding disorder in children. Some writers tested these medications for MET in children [1]. The efficacy of tamsulosin was studied for the treatment of DUS in children by [3].

Silodosin binds to the α-receptor subtype similarly to tamsulosin, but has a 17-fold higher affinity for the α-receptor subtype [1,28]. Silodosin outperformed tamsulosin and doxazosin in treating pediatric urolithiasis, as expected [32]. Subgroup analysis revealed that stones measuring <5mm had significantly better expulsion rate and duration, whereas those measuring >5mm did not show any significant difference. In summary, a-adrenergic blockers can improve stone

ejection efficiency, particularly for smaller stones, contrary to existing standards [3422]. This trial comprised patients treated with a-adrenergic blockers (tamsulosin, doxazosin), as well as calcium channel blockers and adjuvant medicines [1,22]. The article's conclusion was not persuasive due to inadequate data and potential publication bias. The earlier trial on a-adrenergic blockers in juvenile urolithiasis did not provide conclusive results. [26] Our study discovered that a-adrenergic blockers outperformed placebo in terms of expulsion time, which was not observed in the previous review. Furthermore, tamsulosin had higher adverse effects than placebo in our trial. Our study investigated additional variables, such as pain episodes, analgesia need, and stone sizes, which were overlooked in the prior research. This study aims to improve treatment selection in juvenile urolithiasis by correcting previous erroneous findings and providing comparisons. For the first time, we found silodosin to be more effective than tamsulosin in treating pediatric urolithiasis.

5. Conclusion

Our study found that a-adrenergic blockers can improve stone ejection efficiency in juvenile urolithiasis, particularly for tiny stones less than 5mm, with a good safety profile. Further research is needed to determine whether silodosin was the most effective medicine for improving expulsion rates

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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