ORIGINAL ARTICLE

EFFICACY OF ALPHA-ADRENERGIC RECEPTOR ANTAGONISTS IN THE TREATMENT OF DISTAL URETERIC STONES: A PAEDIATRIC STUDY

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Background: European association of urology (EAU) recommended α- blockers for managing distal ureteric stones in the paediatric population. This paper will help to understand the efficacy of Silodosin as a medical expulsive agent for distal ureteric stones in children, along with the required time duration of stone expulsion. **Methods:** Forty participants were enrolled and evaluated for complaints, pain severity, associated symptoms, and ultrasound was done to confirm the position and size of the distal stone. Follow-ups were scheduled after every 7 days (1 week) for redo ultrasound and assessment of the stone position. Data was entered and analyzed in the SPSS version 23. To evaluate the significance of data chi-square test was performed, *p*-value <0.005 was considered significant. **Results:** The minimum and maximum age limits recorded are 3 years and 18 years respectively with a mean age of 9.5±4.5 years and mean stone size was measured as 0.6±0.1 cm. Distribution of stone size indicated the minimum size of 0.4 cm and maximum of 1.0 cm stone in study subjects. Maximum stone expulsion was reported within 14 days or an initial 2 follow-up scans. **Conclusion:** The efficacy of Silodosin and medical expulsive therapy evaluated the effect on pain management as pain episodes declined with Silodosin treatment and spontaneous passage of stones were increased within the first 14 days of treatment. This study will be a beneficial contribution in literature especially in a developing country population where paediatric urolithiasis is on expansion and ongoing

Keywords: Silodosin as MET; Distal ureteric stones; Medical expulsive therapy; Paediatric urolithiasis

Citation: Brohi IB, Bhatti MS, Siyal RA, Ali F, Kaimkhani Z, Laghari HR Efficacy of alpha-adrenergic receptor antagonists in the treatment of distal ureteric stones: a paediatric study. J Ayub Med Coll Abbottabad 2022;34(4):807–11.

DOI: 10.55519/JAMC-04-10379

INTRODUCTION

Urolithiasis is the third most commonly reported urinary tract disorder after urinary tract infection and benign prostate hyperplasia.[1] Within the paediatric population the incident rates have increased in the last 25 years with 1-2% of the adult population. Kidney diseases refer to patients of all ages, a 4 days old neonate with renal stones has been reported in the literature.[2] Ureteric stone management has been considered challenging in the paediatric population, the presence of invasive and non-invasive methods to extract stones are known for years including extracorporeal shockwave lithotripsy (ESWL) and ureteroscopy (URS).[3] Invasive procedures to remove stones are financial strain on low income families, complications related to surgery are another point of concern.[4] MET decreases the chances of invasive and non-invasive procedures such as Ureteroscopy (URS) and extracorporeal shockwave lithotripsy (ESWL) decreasing usage of healthcare usage and minimalizing unnecessary financial burden.[5] Ureteric stones usually pass through the urethra with or without showing complications such as pain, although the stone location, stone size, degree of hydronephrosis, perinephric straining, and severity of pain are a few deciding factors to assess the possibility of medical expulsive therapy or invasive procedures.[6] Many studies specified the benefits of medical expulsive therapy in small stones (≤0.8 cm) present in ureters,[7,8] the limitation of these researches is targeted population was adults (<18 years of age). Medical expulsive therapy (MET) helps in declining the duration of ureteric stones symptoms and corresponding complications including hyderonephrosis, kidney function impairment, and urinary tract infections. Leading professional societies specified contemporary treatment options of alpha-adrenergic receptor antagonists (Silodosin) as an initial treatment option for ureteric stone expulsion for <1 cm stone size without any associated complication and controlled symptoms.[9] This treatment efficacy has been endorsed with many studies indicating increased chances of stone passage in patients treated with alpha-adrenergic receptor antagonists in the adult population.[10,11] European association of urology (EAU) recommended α-blockers for managing distal ureteric stones in the paediatric population, tamsulosin is known as the most common and proven α- adrenergic receptor

blocker for efficacy and safety.[3] While Silodosin is a α1a- adrenergic receptor antagonist and is more selective as compared to tamsulosin for stone expulsion in adults and children located in distal ureters proven by many studies.[11] In Pakistan, MET studies have been conducted with consideration of all α- blockers on adult population[12] this paper will help understand the efficacy of Silodosin as a medical expulsive agent for distal ureteric stones in children, along with the required time duration of stone expulsion. We will also assess the associated factors contributing to stone movement within the ureter and other effects. This study will help paediatric urologists to interpret the usefulness of Silodosin to treat distal ureteric stones in children.

MATERIAL AND METHODS

This is a prospective, cross-sectional study, conducted in the department of paediatric surgery and urology GIMS (Gambat Pir Abdul Qadir Shah Jelani) institute of medical sciences, Gambat District Khairpur, after getting ethical approval (approval letter # PAQSJIMS/MC/458) from the institutional research committee, study data was collected from July till October 2021. All parents or legal guardians were provided with informed consent with a clear statement regarding Silodosin as selected α_{1A} Adrenoceptor antagonist, its use as medical expulsive therapy in children, associated outcomes, and adverse responses with prescribed dosage of 4mg 1×HS. Parents were assured about their free will to accept or reject the proposed treatment option.

Inclusion Criteria: Single ≤ 10mm, distal ureteric stones were included in the study.

Exclusion Criteria: Multiple Renal or ureteric stones, Stones present in proximal or mid ureter, and stone size larger than >10 mm, complain of severe pain or haematuria were excluded from the study.

Total 68 patients were enrolled in the study, of which only 40 patients were studied as the rest were not meeting the inclusion criteria. Presenting complaints were documented along with complete history, Ultrasonography was used as an imaging technique and single distal ureteric stones in patients under the age of 18 years were included in the study.

Patients with multiple stones in the ureter, proximal ureteric stones, mid ureteric stones, renal stones, recurrent stone disease, gross hydronephrosis, or any associated complication were excluded from the study. Upon signing the consent form by parents or guardians, patients were started with conservative Silodosin treatment till stone expulsion or a maximum of 4 weeks duration. Each enrolled participant was evaluated for physical examination, complaints, pain severity, associated symptoms, and ultrasound was done to confirm the position and size of the distal stone. Follow-ups were scheduled after every 7 days (1 week) for redo ultrasound and assessment of the stone position. Within the duration of Silodosin treatment, patients were assessed for pain management, emergency room visits for pain or any other problem, episodes of pain, and any other reported complications such as dysuria, anuria, nausea, vomiting, urgency, and burning micturition. Reported haematuria and anuria were treated immediately. Maximum follow-up duration was decided for 4 weeks, failure of stone expulsion within 4 weeks will lead to ureteroscopy of the patient. The primary endpoint of this study was to evaluate the stone expulsion rate with Silodosin, the secondary endpoint was to analyze associated factors of Silodosin treatment success or failure, episodes of pain, emergency room visits, and associated complications included Lower urinary tract symptoms. To confirm the stone expulsion, ultrasonography was performed. Data was entered and analyzed in the statistical package of social sciences version 23, frequencies and percentages were calculated. To evaluate the significance of data chi-square test was performed, *p*-value <0.005 was considered significant.

RESULTS

Study participants were 40 in number, with an age limit of 18 years. The minimum and maximum age limits recorded are 3 years and 18 years respectively with a mean age of 9.5±4.5 years. The gender distribution of subjects was randomized and 26 (63.4%) males while 14 (34.1%) female participants were enrolled. Weight in kgs was documented, mean weight of study participants was 20.5±8.03 kg, and mean stone size was measured as 0.6±0.1 cm. Distribution of stone size indicated the minimum size of 0.4 cm and maximum of 1.0 cm stone in study subjects. (Figure-1)

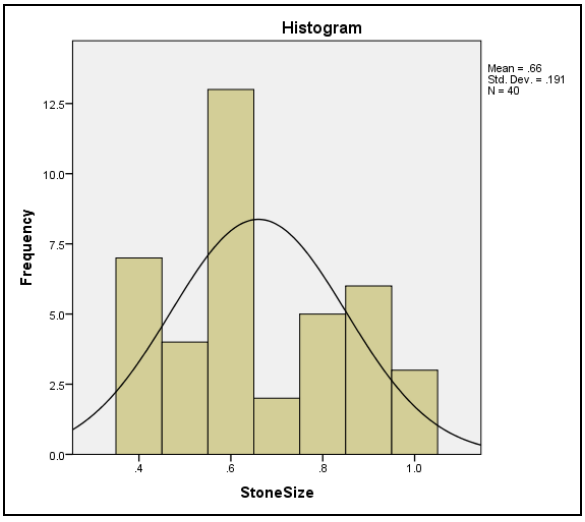

Figure-1: Distribution of stone size in study participants

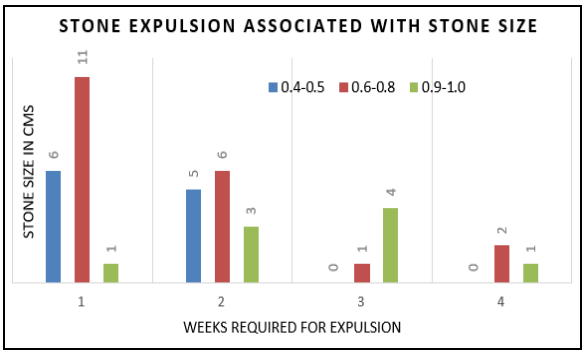

Figure-2: Distribution of weeks required for stone expulsion

Stone sites indicated 32 (78%) right ureteric stones and 8 (19.5%) left ureteric stone, as all subjects had distal ureteric stones, the location was categorized within 4 groups, 3 (7.3%) participants had a stone at Vesico-ureter junction, 4 (9.8%) subjects had a stone at pyramid distal ureter, 7 (17.1%) subjects indicated stone position at mid distal ureter and 254 (61%) had a stone at distal ureter position. Stone location was categorized and assessed with follow up scans the presenting day location was changed on the first week follow up, only 1 (2.4%) stone was present in pyramid distal ureter while the remaining 3 moved towards Distal ureter, similarly 4 (9.8%) out of 7 (17.1%) stones moved from mid distal ureter to distal ureter within first 7 days of treatment. 25 (61%) distal ureteric stones were increased and 31 (75.6%) stones were reported in the first follow-up scan, While Vesico-ureter junction stones were increased in numbers from 3 (7.3%) to 4 (9.8%). Proceeding to second follow up after 14 days, pyramid distal ureter and mid distal ureter had no stone left, while distal ureter stones were visible only in 6 (14.6%) participants, and Vesico-ureter junction had 2 (4.9%) stones. The remaining stones were expelled within 14 days, showing 80% clearance rates. 3rd-week follow-up indicated a 100% clearance rate with no visible stone in the distal ureter. (Table-1)

Maximum stone expulsion was reported within 14 days or an initial 2 follow-up scans, Data was analyzed to evaluate the association of stone size on stone expulsion duration. Stones were categorized within three groups, group 1 had stones measuring 0.4–0.5 cm in 11 (27.5%) patients, and group 2 had stones with 0.6–0.8 cm size in 20 (50%) patients while group 3 had 0.9-1.0 cm size stones in 9 (22.5%) patients. Group 1 showed 100% clearance in 2 weeks, group 2 showed approximately 75% clearance in the first 2 weeks, and 100% clearance in 4 weeks. Although group 3 showed maximum clearance (80%) in the 2nd and 3rd week of treatment. (Figure-2)

Complications such as pain management, episodes of pain, visit to the emergency room, nausea, and Lower urinary tract symptoms including dysuria, urgency, burning micturition were analyzed with the association of age difference, stone location, and stone size. Results specified fair pain management in older participants <7 years, while pain management declines with increasing stone size. Emergency room visits reported maximum in older patients with large size (0.9–1.0 cm) stone, Lower urinary tract symptoms were reported in young patients more frequently as compared to older patients. (Table-2, 3 & 4)

Table-1: Stone position within treatment days

Variables		Presenting day	1st week follow up	2nd week follow up	*p*-value
Stone position	Paramid distal ureter	4 (9.8%)	1 (2.4%)	0	0.03
	Mid distal ureter	7 (17.1%)	4 (9.8%)	0	0.07
	Distal Ureter	25 (61%)	31 (75.6%)	6 (14.6%)	0.04
	VUJ	3 (7.3%)	4 (9.8%)	2 (4.9%)	0.8

Table-2: Association of complications with Age of study participants.

Variables		Age Distribution		
		1 to 10	13 to 18	*p* value
Pain management	Fair	17	11	0.2
	Good	10	2	
Episodes of pain	≤ 2	9	10	0.3
	≤ 4	10	3	
ER visits	≤ 2	3	3	0.7
	≤ 4	1	0	
Side effects	Dysuria	4	0	0.3
	Nausea	1	0	
	Burning Micturition	1	0	
	Urgency	0	1	

Table-3: Association of complications with stone location.

Variables		Stone location				
		VUJ	Distal Ureter	Mid distal Ureter	Para-mid distal ureter	*p*- value
Pain management	Fair	1	22	3	1	0.01
	Good	2	3	4	3	
Episodes of pain	≤ 2	2	18	4	2	0.35
	≤ 4	0	2	1	1	
ER visits	≤ 2	1	3	1	2	0.05
	≤ 4	0	0	0	0	
Side effects	Dysuria	0	0	2	2	0.01
	Nausea	0	0	1	0	
	Burning Micturition	1	0	0	0	
	Urgency	0	1	0	0	

Table-4: Association of complications with stone size.

Variables		Stone size		
		≤ 0.5	0.6-1.0	*p* value
Pain management	Fair	10	18	0.9
	Good	4	8	
Episodes of pain	≤ 2	7	12	0.04
	≤ 4	3	10	
ER visits	≤ 2	2	4	0.1
	≤ 4	0	1	
Side effects	Dysuria	2	4	0.2
	Nausea	1	1	
	Burning Micturition	1	0	
	Urgency	1	0	

DISCUSSION

Distal ureteric stones are been treated with open surgeries to minimally invasive procedures, such as URS, ESWL, etc, although all of these treatment options have the risk of complications such as Urinary tract infections, ureteric colic, and increased hyderonephrosis.[13] The paediatric population with renal stones is prone to get recurrent stone formation, therefore needs multiple interventions in their lifetime. To minimize the risk of these complications, medical expulsive therapy has again the status of treatment of choice to exorcise distal ureteric stones conservatively.[9] MET improves the chances of spontaneous passage of ureteric stone with less risk of complications.[3] α-blockers are known as a superior MET drug as compared to calcium channel inhibitors, as colic episodes are decreased with α-blocker treatment. In the paediatric population, the main reason for using MET instead of interventional treatment options is to decrease ureteric muscle spasms, reduce pain and save patients with unnecessary pain and risk of complication associated with invasive procedures.[14] α-Adrenoceptor are mainly located in distal ureteric walls and blocking these receptors may decrease smooth muscle contractions resulting in fewer pain episodes and spontaneous stone passage.[15] Silodosin has been selected as the drug of choice for this study as it is known to be the best α_{1A}- Adrenoceptor blocker, as it can affect distal ureteric stone passage duration and has no risk of elevating blood pressure in paediatric subjects, Usage of Silodosin in paediatric subjects reduces the chances of pain episodes therefore use of analgesics can be minimized.[16] The present study results indicated 80% stone-free rates at the first 2 weeks of treatment, a study from Egypt analyzing the effect of Silodosin in the paediatric population showed a 72.2% stone-free rate in 2 weeks, 2.3 % pain episodes.[17] study of Silodosin as MET in children indicated 88% stone-free rates while tamsulosin showed 64% stone-free rates with a *p*-value of <0.01.[18] The duration of stone expulsion is shorter with Silodosin as MET, in our study, the maximum required days to expel 1.0 cm stone were recorded as 21–22 days, similarly the study of turkey indicated 18–20 days for 100% clearance of stone measuring 1.0 cm. Similarly the episodes of pain are decreased in patients with stone size measuring between 0.5–1.0 cm were higher than stone sizes measuring 0.4 cm, similar results have been showing by other studies too[19,20] The adverse effects reported in previous studies were only drug-related complications including headache and dizziness in mild severity while our study subjects reported decline lower urinary tract symptoms intensity with Silodosin,[16,21] Visits to emergency rooms were recorded in our study and evaluated as the need for intramuscular or intravenous analgesics to reduce pain, the study participants showed fewer visits with the smaller size of stones. Meta-analysis describing the efficacy of Silodosin and medical expulsive therapy evaluated the effect on pain management as pain episodes declined with Silodosin treatment and spontaneous passage of stones were increased within the first 14 days of treatment.[5,22,23] Silodosin has not been fully evaluated in the paediatric population as medical expulsive therapy, this study will be a beneficial contribution in literature especially in a developing country population where paediatric

urolithiasis is on expansion and ongoing. The limitations of this study are a smaller sample size, and no CT KUB has been performed to assess the ureteric stones due to financial restraints. However, a multi-center study with large sample size and more advanced imaging techniques to analyze ureteric stone position is recommended in a similar population.

CONCLUSION

Our data indicated that Silodosin suggestively helps the passage of distal ureteral stones measuring <10mm and relieves renal colic, therefore, reduces the need for an invasive procedure and risk of surgery-related complications. Silodosin can safely be used as medical expulsive therapy for distal ureteric stone in children.

Acknowledgment: All the Staff of GIMS, GAMBAT

Conflict of Interest: None.

Limitations of study: Multicenter study with larger sample size is required for more detailed inference of Silodosin, comparing other medical expulsive therapy agent is also recommended for accurate difference of days required for expulsion and complications reported.

AUTHORS' CONTRIBUTION

IBB: Objective, in charge study, proof reading. MSB: Introduction write-up. RA: Data analysis and interpretation. FA: Discussion, write-up. ZK: Research ethics person. HR: Initial proof reading, ERC correspondence.

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Submitted: November 11, 2021	*Revised: May 23, 2022*	*Accepted: May 23, 2022*

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