Published in final edited form as:

J Urol. 2014 August ; 192(2): 506–511. doi:10.1016/j.juro.2014.01.091.

Tamsulosin and the spontaneous passage of ureteral stones in children: A multi-institutional cohort study

Gregory E. Tasian, MD, MSc^{1,2}, Nicholas G. Cost, MD^{3,4}, Candace F. Granberg, MD⁵, Jose E. Pulido², Marcelino Rivera, MD⁵, Zeyad Schwen⁶, Marion Schulte, RN⁴, and Janelle A. Fox, MD^{6,7}

¹Department of Surgery, Division of Pediatric Urology, The Children's Hospital of Philadelphia; Philadelphia, Pennsylvania

²Perelman School of Medicine at The University of Pennsylvania; Philadelphia, Pennsylvania

³Department of Surgery, Division of Urology, Colorado Children's Hospital; Denver, Colorado; Denver, Colorado

⁴Division of Urology, Cincinnati Children's Hospital, Cincinnati, OH

⁵Department of Urology, Mayo Clinic; Rochester, Minnesota

⁶University of Pittsburgh School of Medicine; Pittsburgh, Pennsylvania

⁷Department of Urology, Lieutenant Commander; Naval Medical Center Portsmouth, Portsmouth, Virginia

Abstract

Purpose—Tamsulosin is associated with increased passage of ureteral stones in adults, but its effectiveness in children is uncertain. We determined the association between tamsulosin and the spontaneous passage of ureteral stones in children.

Methods—We performed a multi-institutional retrospective cohort study of children 18 years who presented between 2007 and 2012 with a ureteral stone 10 mm and were managed with tamsulosin or oral analgesics alone. The outcome was spontaneous stone passage defined as radiographic clearance and/or patient report of passage. Subjects prescribed tamsulosin were matched with subjects prescribed analgesics alone using nearest neighbor propensity score matching to adjust for treatment selection. Conditional logistic regression models were used to estimate the association between tamsulosin and spontaneous passage of ureteral stones, adjusting for stone size and location.

Corresponding Author: Gregory E. Tasian, MD, MSc, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Department of Surgery, Division of Urology, 3rd Floor- Wood Center, Philadelphia, PA 19104-4399, Phone: 215.590.0317, Fax 215.590.3985, tasiang@chop.edu.

Dr Fox has the following disclaimer as a military service member: Dr. Fox is a military service member (or employee of the U.S. Government). This work was prepared as part of my official duties. Title 17, USC, §105 provides that 'Copyright protection under this title is not available for any work of the U.S. Government.' Title 17, USC, §101 defines a U.S. Government work as a work prepared by a military service member or employee of the U.S. Government as part of that person's official duties.' The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, or the United States government.

Results—Of 449 children with ureteral stones, 334 were eligible for inclusion, and complete data were available for 274 children from 4 institutions (99 tamsulosin; 175 analgesics alone). Following case matching, there were no differences in patient age, gender, weight, height, stone size, or stone location between the 99 subjects prescribed tamsulosin and the 99 propensity-score matched subjects prescribed analgesics alone. In the tamsulosin cohort, 55% of ureteral stones passed versus 44% in the analgesics alone cohort ($p = 0.03$). In multivariate analysis adjusting for stone size and location, tamsulosin was associated with spontaneous passage of ureteral stones (OR 3.31; 95% CI 1.49–7.34).

Conclusions—The odds of spontaneous passage of ureteral stones were higher in children prescribed tamsulosin versus analgesics alone.

Keywords

Nephrolithiasis; tamsulosin; comparative effectiveness

Introduction

Nephrolithiasis has become increasingly common in children. Among adolescents, the incidence of nephrolithiasis has increased approximately 6–10% annually over the last 20 years.^{1, 2} The emergence of nephrolithiasis as a pediatric disease has resulted in a need to determine the optimal treatment strategies for children with kidney stones.

In adults, alpha-blockers increase the spontaneous passage rates of ureteral stones,³ decrease time to stone passage,⁴ and decrease analgesic requirements.^{4, 5} Furthermore, alpha-blockers used as medical expulsive therapy (MET) for distal ureteral stones in adults is cost-effective relative to analgesics alone.⁶ However, few studies have assessed the efficacy of MET for ureteral stones in children. A study in 2009 failed to demonstrate any improvement in passage of distal ureteral stones in children treated with doxazosin.⁷ However, this study was likely underpowered to detect a clinically important and statistically significant effect. Subsequently, Mokhless and colleagues observed tamsulosin increased stone passage in children. However, this study was limited by including children who had retained ureteral stones following lithotripsy or percutaneous nephrolithotomy in the tamsulosin group, but not in the placebo group.⁸ It is possible that the spontaneous passage rates of residual fragments after surgery are different than newly diagnosed stones. Additionally, these studies excluded children with stones in the proximal or mid ureter, which limits their generalizability. Consequently, the effectiveness of tamsulosin in increasing the spontaneous passage of ureteral stones in children who present with new symptomatic ureteral stones is uncertain.

We report the results of a multi-institutional retrospective cohort study designed to determine the association between tamsulosin and the spontaneous passage of ureteral stones in children. We hypothesized that tamsulosin increases spontaneous passage of ureteral stones in children.

Methods

Patient cohort description and study design

This was a multi-institutional retrospective cohort study. Research data were derived from approved Children's Hospital of Philadelphia, Children's Hospital of Pittsburgh of UPMC, Cincinnati Children's Hospital and Mayo Clinic IRB protocols. Potentially eligible subjects were male and female children aged 2–18 years who presented between January 1, 2007 and December 31, 2012 to the Emergency Department (ED), outpatient Urology clinic, or the inpatient Urology hospital consult service with a ureteral stone, and were prescribed either tamsulosin and oral analgesics or oral analgesics alone. We chose 2007 as the study start date because MET was gaining acceptance for management of ureteral stones in children at our institutions at that time. Potentially eligible patients were identified by searching outpatient and hospital billing databases for nephrolithiasis ICD-9 codes (592, 592.1, 592.9) at each study site.

We excluded patients who underwent surgical intervention within 24 hours of presentation, patients with a history of ureteral or kidney surgery, stones >10mm, and those with a clinical contraindication to a trial of stone passage. Contraindications included urinary tract infection (temperature > 38°C and/or positive urine culture), solitary kidney, immunocompromised status (oncology patient, daily steroids, bone marrow or solid organ transplant, absolute neutrophil count <500, or active use of an immunomodulator drug), renal insufficiency (estimated GFR < 60ml/min as estimated by nuclear GFR, cystatin C, or bedside Schwartz formula), and/or contraindication to tamsulosin (e.g. sulfa allergy). Data were abstracted using manual chart review, which was performed separately at each study site. Subjects with missing data were excluded from the analyses.

Outcome definition

The primary outcome was spontaneous passage of a ureteral stone. Passage was defined as radiographic clearance and/or patient report of passage. All those who did not pass stones within 6 weeks underwent either ureteral stent placement and/or ureteroscopy. Additional indications for surgical management prior included pain refractory to oral analgesics and/or repeat visits to the ED.

Exposure variable and covariates

The cohort-defining variable was prescription of tamsulosin 0.4mg daily as documented by consultation or clinic notes, or ED discharge documents. The capsule was broken and the drug was sprinkled into a drink, yogurt, or pudding for those children who could not swallow the capsule. Covariates included age, height, weight, symptoms on presentation (pain, vomiting, hematuria, voiding symptoms), stone size (mm), and stone location. Stone location was a categorical variable defined as: ureteropelvic junction, mid-ureteral, and ureterovesical junction. Ultrasound, CT, and/or abdominal x-ray were used to confirm stone size and location.

Sample Size Calculation

At 80% power and two-sided $\alpha = 0.05$, 160 subjects (80 per study group) would be needed to detect a 15% difference in the frequency of spontaneous stone passage between subjects who did and did not receive tamsulosin.

Propensity Score Matching

A panel of 4 pediatric urologists (GET, NGC, CFG, JAF) identified patient and stone characteristics that could influence the decision to prescribe tamsulosin for a child with a ureteral stone. Characteristics identified were age, gender, height, and weight, and stone size and stone location. These independent variables were included in a logistic regression model with tamsulosin prescription as the dependent variable. Age, height, and weight were analyzed as continuous variables. Stone size was grouped into 4 strata: < 3mm, 3–5mm, >5–7mm, and >7–10mm. Size was analyzed as a categorical variable to facilitate matching and allow further exploration of an association between size and passage in regression analyses. Stone location was analyzed as a categorical variable as described above. The resultant beta coefficients represented the propensity score, or the probability of tamsulosin prescription.

Children prescribed tamsulosin were matched to children prescribed analgesics on the basis of the propensity score using nearest neighbor matching with replacement. After sorting all subjects on their propensity score, each subject who received tamsulosin was matched to the subject with the closest propensity score who was treated with analgesics alone. We allowed a maximum distance of 0.2 between the propensity scores of the tamsulosin and control subjects. This method of matching within a distance of 0.2 in the logit of the propensity score has been shown to perform better than other methods.⁹

Statistical Analysis

We compared non-parametric continuous variables using the rank-sum test, parametric variables using t-tests, and categorical variables using the chi-square test. Following case matching, unadjusted differences in stone passage between the two groups were evaluated using McNemar's test. The association between tamsulosin and stone passage was evaluated using multivariate conditional logistic regression. We included stone size as a continuous variable and stone location as an ordinal variable in the final model. As a sensitivity analysis, patient age, gender, weight, and height were added to the model to evaluate for residual confounding of the association between tamsulosin and stone passage. Confounding was defined as a change of 15% between the unadjusted and adjusted odds ratio for stone passage.

All analyses were performed according to the intention-to-treat principle. Tests were 2-sided, and statistical significance was defined as $p < .05$. All analyses were performed with Stata 13 (StataCorp, College Station, TX). This study was approved by the Institutional Review Boards at each participating institution.

Results

Description of Study Population

Between 2007 and 2012, 449 children with ureteral stones were treated at our institutions and were assessed for eligibility. After applying inclusion and exclusion criteria, 99 children were in the tamsulosin cohort and 175 were in the analgesics alone cohort (Figure). Most patients presented with pain and vomiting. CT was used most frequently to diagnose the stones in each group. Baseline patient and stone characteristics of the population with complete data are shown in Table 1. Mean duration between presentation and last Urology clinic appointment was 8 months.

Unadjusted Outcomes

In the total population of 274 children with complete data prior to case-matching, subjects prescribed tamsulosin were older and taller, and had smaller, more distal stones. In the tamsulosin cohort, 58% of stones passed versus 41% in children prescribed analgesics alone ($p = 0.06$). Relative to stones at the UPJ, stones at the UVJ ($p = 0.001$) and smaller stones ($p < 0.001$) were more likely to pass. Age, gender, weight, and height were not associated with stone passage.

Propensity-Score Matched Analysis

Following case-matching, there were no differences in any patient or stone characteristics between the subjects prescribed tamsulosin and subjects prescribed analgesics alone (Table 2). Using McNemar's test, 56% of ureteral stones passed in the tamsulosin cohort, and 44% in the analgesics alone cohort ($p = 0.03$). In multivariate conditional regression analysis, adjusting for stone size and location, tamsulosin was associated with spontaneous passage of ureteral stones (OR 3.31; 95% CI 1.49–7.34). The adjusted odds ratios of stone passage associated with tamsulosin, stone size, and stone location are shown in Table 3. Adding age, gender, height, and weight to the model did not demonstrate any confounding effect on the association between tamsulosin and stone passage. No adverse reactions to tamsulosin were observed.

Discussion

In this multi-institutional retrospective cohort study, the odds of spontaneous passage of ureteral stones were over three times higher in children prescribed tamsulosin than those prescribed oral analgesics alone, controlling for patient age, gender, height, and weight, as well as stone size and location. No adverse side effects associated with tamsulosin were noted. Although bias and confounding can occur in all observational studies, the stability of the observed effect of tamsulosin on stone passage before and after propensity score matching, suggests that tamsulosin increases the spontaneous passage of ureteral stones in children.

Studies of the efficacy of MET in children with ureteral calculi are limited, making it difficult to compare our findings to the existing literature. To our knowledge, there has been only one published study that analyzed whether tamsulosin increased passage of ureteral

calculi in children. In this randomized trial of tamsulosin versus placebo in children with distal ureteral stones up to 12mm, Mokhless *et al.* demonstrated improved time to stone passage of 8.2 versus 14.5 days in the tamsulosin versus placebo groups, respectively.⁸ However, differences in the inclusion criteria between those receiving tamsulosin and placebo limit the conclusions that can be drawn from this study. Among adults, the efficacy of tamsulosin is mixed, but generally favors an effect of tamsulosin on stone passage. A meta-analysis of randomized trials demonstrated that tamsulosin increased stone passage.³ However, differences in the trial design, length of follow-up, use of adjuvant therapies such as corticosteroids and NSAIDS, and determination of stone-free status among the included studies limit the conclusions that can be drawn from the pooled results.^{10–14} More recent well-designed studies have not demonstrated that tamsulosin improved passage of stones or decreased the time to stone passage. However, the small sizes of the stones may have limited the power of these studies to detect a statistically significant and clinically important difference.^{15, 16} As suggested by this lack of efficacy for small stones seen in adult trials, it is possible that tamsulosin is most effective for “intermediate” sized stones. In other words, tamsulosin may not increase the passage of small (e.g. <3mm) distal stones for which the probability of spontaneous passage is already high. Our study was not powered to detect effect modification of tamsulosin by stone size. Additionally, we were not able to evaluate the time to stone passage or the analgesic requirements due to poor recording of these data in this retrospective study. Additional studies are needed to identify patient and stone features, including characteristics that may be unique to children that predict tamsulosin efficacy.

No adverse side effects associated with tamsulosin were noted, which is consistent with prior studies. Similarly, Mokhless *et al.* reported no adverse symptoms that led to drug discontinuation when tamsulosin 0.4 mg was prescribed for children older than 4 years old and 0.2 mg was prescribed for children 4 years old or younger.⁸ Additionally, tamsulosin was studied in 52 patients between 3.5 and 17.8 years of age with primary bladder neck dysfunction. Blood pressure and heart rate were monitored at every visit over a mean follow-up of 46 months. Two patients reported light-headedness and somnolence, but no patient had any major side effects while on tamsulosin.¹⁷

This study benefits from a cohort drawn from four institutions, which increases the generalizability of our observations. Additionally, we used methods to decrease selection bias and confounding, which may be present in all observational studies. In randomized controlled trials, the randomization process balances observed and unobserved confounders between the treatment and control groups. However, in observational studies such as this, treatment selection is often influenced by characteristics of the patients. This can result in selection bias, such that systematic differences exist between treated subjects and untreated subjects. We mitigated this bias by conditioning on propensity scores, which results in less biased estimation of the difference in observed responses to two treatments.¹⁸ After propensity score matching, the patient and stone characteristics of between the tamsulosin and analgesic alone cohorts were similar. Furthermore, our analysis adjusted for other potential confounders such as age, height, and use of ibuprofen.

We acknowledge the limitations of this study. First, misclassification of treatment status is possible since we cannot be certain that patients prescribed tamsulosin actually took the medication. This would lead to underestimating differences in stone passage between the cohorts since failure to take tamsulosin would make the two groups more similar. Second, both CT and ultrasound, which differ in their ability to characterize kidney stones,^{19, 20} were used to determine stone location and size. CT and ultrasound use were similar between the cohorts. Thus any misclassification of stone size should be balanced between the two groups. Third, we did not have centralized or standardized review of diagnostic imaging to confirm stone size and location. There therefore may have been variation in imaging interpretation between sites and providers. However, we do not expect any variation that would be clinically relevant given the broad categories of stone size and location we used. Fourth, the period of time over which a stone could spontaneously pass was not defined. Consequently, it is possible that the thresholds of the treating physicians for allowing stone passage may differ and that some children who were going to pass their stones instead underwent surgery. However, in order to be a significant confounder of the effect of tamsulosin, the threshold for surgical intervention would have to be associated with whether or not the patient was prescribed tamsulosin. Although this is possible, it seems unlikely. Finally, our outcome was determined by self reported stone passage and/or radiologic confirmation done at the discretion of the treating physician. Accordingly, the dates of stone expulsion were poorly recorded, which precluded any time-to-event analyses. Future studies should standardize methods to confirm stone passage at defined periods of time from stone occurrence and upon self-reported passage, which would allow determination of the effect of tamsulosin on time to stone passage.

Our observations need to be validated in a prospective randomized trial with clearly defined inclusion and exclusion criteria. Such a study should be powered to determine patient and stone characteristics for which tamsulosin use is most beneficial. It is unlikely that such a trial could be conducted in a single center given the relatively low (but rising) incidence of kidney stones in children. Continued collaborative efforts are necessary to determine the optimal treatments for children with kidney stones. Until these studies are performed, the increased stone passage and lack of adverse side effects supports use of tamsulosin for children with ureteral stones.

Conclusions

The odds of spontaneous passage of ureteral stones were higher in children prescribed tamsulosin versus analgesics alone. A randomized controlled trial should be performed to validate these observations.

Acknowledgments

Dr Tasian was supported by NIH-T32HD060550. The National Institutes of Health had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication. We thank Angela Kalmus for abstracting the data for children managed at The Children's Hospital of Philadelphia.

References

1. Dwyer ME, Krambeck AE, Bergstralh EJ, et al. Temporal trends in incidence of kidney stones among children: a 25-year population based study. *J Urol.* 2012; 188:247. [PubMed: 22595060]
2. Routh JC, Graham DA, Nelson CP. Epidemiological trends in pediatric urolithiasis at United States freestanding pediatric hospitals. *J Urol.* 2010; 184:1100. [PubMed: 20650479]
3. Hollingsworth JM, Rogers MAM, Kaufman SR, et al. Medical therapy to facilitate urinary stone passage: a meta-analysis. *Lancet.* 2006; 368:1171. [PubMed: 17011944]
4. Pedro RN, Hinck B, Hendlin K, et al. Alfuzosin stone expulsion therapy for distal ureteral calculi: a double-blind, placebo controlled study. *J Urol.* 2008; 179:2244. [PubMed: 18423747]
5. Hermanns T, Sauermann P, Rufibach K, et al. Is there a role for tamsulosin in the treatment of distal ureteral stones of 7 mm or less? Results of a randomised, double-blind, placebo-controlled trial. *Eur Urol.* 2009; 56:407. [PubMed: 19375849]
6. Bensalah K, Pearle M, Lotan Y. Cost-effectiveness of medical expulsive therapy using alpha-blockers for the treatment of distal ureteral stones. *Eur Urol.* 2008; 53:411. [PubMed: 17889988]
7. Aydogdu O, Burgu B, Gucuk A, et al. Effectiveness of doxazosin in treatment of distal ureteral stones in children. *The Journal of urology.* 2009; 182:2880. [PubMed: 19846149]
8. Mokhless I, Zahran A-R, Youssif M, et al. Tamsulosin for the management of distal ureteral stones in children: A prospective randomized study. *Journal of pediatric urology.* 2011; 1
9. Austin PC. The performance of different propensity score methods for estimating marginal odds ratios. *Stat Med.* 2007; 26:3078. [PubMed: 17187347]
10. Dellabella M, Milanese G, Muzzonigro G. Efficacy of tamsulosin in the medical management of juxtavesical ureteral stones. *J Urol.* 2003; 170:2202. [PubMed: 14634379]
11. Dellabella M, Milanese G, Muzzonigro G. Randomized trial of the efficacy of tamsulosin, nifedipine and phloroglucinol in medical expulsive therapy for distal ureteral calculi. *J Urol.* 2005; 174:167. [PubMed: 15947613]
12. Kupeli B, Irkilata L, Gurocak S, et al. Does tamsulosin enhance lower ureteral stone clearance with or without shock wave lithotripsy? *Urology.* 2004; 64:1111. [PubMed: 15596181]
13. Yilmaz E, Batislam E, Basar MM, et al. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. *J Urol.* 2005; 173:2010. [PubMed: 15879806]
14. Porpiglia F, Ghignone G, Fiori C, et al. Nifedipine versus tamsulosin for the management of lower ureteral stones. *J Urol.* 2004; 172:568. [PubMed: 15247732]
15. Vincendeau S, Bellissant E, Houlgatte A, et al. Tamsulosin hydrochloride vs placebo for management of distal ureteral stones: a multicentric, randomized, double-blind trial. *Archives of internal medicine.* 2010; 170:2021. [PubMed: 21149761]
16. Ferre RM, Wasielewski JN, Strout TD, et al. Tamsulosin for ureteral stones in the emergency department: a randomized, controlled trial. *Ann Emerg Med.* 2009; 54:432. [PubMed: 19200622]
17. Van Batavia JP, Combs AJ, Horowitz M, et al. Primary bladder neck dysfunction in children and adolescents III: results of long-term alpha-blocker therapy. *J Urol.* 2010; 183:724. [PubMed: 20022041]
18. Rosenbaum PR, Rubin DR. The Central Role of the Propensity Score in Observational Studies for Causal Effects. *Biometrika.* 1983; 70:41.
19. Johnson EK, Faerber GJ, Roberts WW, et al. Are stone protocol computed tomography scans mandatory for children with suspected urinary calculi? *Urology.* 2011; 78:662. [PubMed: 21722946]
20. Passerotti C, Chow JS, Silva A, et al. Ultrasound versus computerized tomography for evaluating urolithiasis. *J Urol.* 2009; 182:1829. [PubMed: 19692054]

Figure.
Cohort flow diagram

Table 1

Characteristics of 273 children with ureteral stones according to treatment group

	Analgesics alone (n = 174)	Tamsulosin (n = 99)	p-value
Age – yr (IQR)	12.1 (9.5–14.8)	14.8 (12–16.7)	< 0.001
Male gender (%)	99 (52)	40 (40)	0.06
Height- m	1.5 (1.4–1.6)	1.6 (1.5–1.7)	< 0.001
Weight- kg (IQR)	42.4 (27.3–62)	51.5 (26.7–64.5)	0.56
Symptoms on presentation			
Pain	167 (97)	98 (99)	0.2
Vomiting	110 (63)	56 (67)	0.55
Hematuria	63 (36)	35 (35)	0.86
Voiding symptoms	40 (23)	17 (17)	0.25
Stone size (IQR)	4 (3–6)	4 (3–5)	0.04
Stone location (%)			0.05
UPJ	72 (41)	32 (32)	
Mid ureter	20 (11)	6 (6)	
UVJ	82 (47)	61 (61)	
Imaging modality used to diagnose ureteral stone			0.59
CT	142 (81)	77 (78)	
Ultrasound	29 (17)	21 (21)	
KUB	3 (2)	1 (1)	

Table 2

Characteristics of 99 matched pairs of children with ureteral stones treated with and without tamsulosin

	Analgesics alone (n = 99)	Tamsulosin (n = 99)	p-value
Age – yr (IQR)	14.6 (11.8–16.1)	14.4 (12–16.7)	0.55
Male gender (%)	39 (39)	40 (40)	0.89
Height- m (IQR)	1.6 (1.5–1.6)	1.6 (1.5–1.7)	0.32
Weight- kg (IQR)	45.5 (32.6–61.3)	51.5 (26.7–64.3)	0.39
Symptoms on presentation			
Pain	99 (100)	98 (99)	0.32
Vomiting	63 (63)	62 (62)	0.89
Hematuria	38 (39)	35 (35)	0.66
Voiding symptoms	17 (17)	17 (17)	
Stone size	3.5 (3–5)	4 (3–5)	0.22
Stone location (%)			0.95
UPJ	32 (32)	32 (2)	
Mid ureter	5 (5)	6 (6)	
UVJ	62 (63)	61 (62)	
Imaging modality used to diagnose ureteral stone			0.09
CT	88 (89)	77(78)	
Ultrasound	11 (11)	21(21)	
KUB	0 (0)	1 (1)	

Table 3

Conditional logistic regression model estimating association between tamsulosin and spontaneous passage of ureteral stones

Predictor Variable	Odds Ratio	95% CI	p
Tamsulosin	3.31	1.49–7.34	0.003
Stone size (mm)	0.58	0.41–0.83	0.003
Stone location			
UPJ	reference		
Mid ureter	1.33	0.42–4.16	0.49
UVJ	2.98	0.35–25.08	0.32