Journal of Pediatric Surgery 55 (2020) 1373–1376

Contents lists available at ScienceDirect

Journal of Pediatric Surgery

journal homepage: www.elsevier.com/locate/jpedsurg

What predicts spontaneous passage of ≤1 cm ureteral stones in children?☆

A. Midhat Elmacı [a], M. İrfan Dönmez [b,*], Fatih Akın [c], Bilal Çetin [d], Metin Gündüz [e]

[a] Ali Kemal Belviranlı, Women's Maternity and Children's Hospital, Pediatric Nephrology, Konya, Turkey
[b] Konya Training and Research Hospital, Pediatric Urology, Konya, Turkey
[c] Necmettin Erbakan University, Faculty of Medicine Department of Pediatrics, Konya, Turkey
[d] Istanbul University Istanbul Faculty of Medicine, Department of Urology, Istanbul, Turkey
[e] Selcuk University Faculty of Medicine, Department of Pediatric Surgery, Konya, Turkey

ARTICLE INFO

Article history:
Received 13 March 2019
Received in revised form 13 May 2019
Accepted 15 May 2019

Keywords:
Urolithiasis
Ureteric stone
Conservative
Spontaneous passage
Pediatric

ABSTRACT

Purpose: The aim of this study is to determine what factors predict spontaneous passage of ≤1 cm ureteral stones in children.
Methods: Files of the patients diagnosed with a single ureteral stone on a given side between 2008 and 2017 were retrospectively reviewed. Patients with congenital obstructive uropathy, neurogenic bladder, vesicoureteral reflux and those with a stone diameter of >1 cm were excluded. Detection of ureteral stones was done using ultrasonography (US) primarily, and computed tomography when US findings were inconclusive. Patients were treated either conservatively or surgically. Conservative treatment included adequate hydration and pain management whereas surgical treatment included ureteroscopic intervention. Apart from those who required urgent intervention, patients were referred for surgical treatment after 2–4 weeks of follow-up with no spontaneous passage. Factors analyzed for association of spontaneous passage included age, gender, type of hematuria, stone localization, laterality, presence of concomitant kidney stone, degree of hydronephrosis, stone size and stone composition.
Results: A total of 70 patients (38 males, 32 females); median age 4.7 years had a ≤1 cm ureteral stone (median diameter 7 mm). US was able to diagnose the ureteric stone in 47 patients while computed tomography was required in 23 patients. Spontaneous passage was observed in 40 patients (57.1%). Median time for stone passage was 8 days (3–34 days). Stone size and presence of hematuria (macroscopic and microscopic combined) were factors associated with spontaneous passage and 6.7 mm was found to be the cut-off (AUC = 0.953; 95% CI 0.905–1.000; sensitivity 96.7%, specificity 82.5%, $p < 0.001$). Moreover, age, degree of hydronephrosis or stone location were not associated with spontaneous passage.
Conclusion: Patients with a ureteric stone size <6.7 mm can safely be followed conservatively, with a spontaneous passage rate of 82.5%.
Type of Study
Case series with no comparison group.
Level of Evidence
IV

Urolithiasis is an important cause of morbidity in both adults and children, with an increasing prevalence worldwide, that may cause renal functional damage, lead to emergency room visits and affect quality of life [1]. The overall incidence of urolithiasis in children is 6–10%, with the majority (~ 5%) being ureterolithiasis [2,3]. Although clinical findings in adults are often more obvious, children are more difficult to diagnose, especially infants and toddlers who may not present with traditional renal colic symptoms [4]. Therefore, it is challenging to diagnose, follow and treat these patients.

Treatment options in children and adolescents with ureteric stones include pain control, medical expulsive therapy (MET) and

☆ **Acknowledgement:** We would like to thank Amanda F. Saltzman, MD (Children's Hospital Colorado) for kindly reviewing the manuscript. **Conflict of Interest:** None. **Funding:** None. **Ethical Standards:** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

* Corresponding author at: Konya Training and Research Hospital, Pediatric Urology, Konya, Turkey. Tel.: +90 533 571 7298; fax: +90 332 323 6723.
E-mail addresses: drmidhat@hotmail.com (A.M. Elmacı), m_irfan83@yahoo.com (M.İ. Dönmez), drfatihakin@gmail.com (F. Akın), bilal_cetin@yahoo.com (B. Çetin), drmetingunduz@yahoo.com (M. Gündüz).

https://doi.org/10.1016/j.jpedsurg.2019.05.012
0022-3468/© 2019 Elsevier Inc. All rights reserved.

interventions such as extracorporeal shock wave lithotripsy (ESWL), ureteroscopy, percutaneous surgery, laparoscopy assisted or open surgery. Similar to adults, treatment strategies are based on stone location, size and clinical and radiological findings [5]. However, spontaneous passage of ureteric stones is possible in pediatric patients. Although predominantly cited in the adult literature, lower stone size, distal stone location, younger age, left sided stones and presence of hydronephrosis have been shown to predict spontaneous stone passage [6–10]. Also, there are studies reporting successful spontaneous passage with medical expulsive therapy, but small patient cohorts and no long-term follow-up limit these studies [11,12].

The evidence for medical expulsive therapy, watchful waiting and spontaneous passage for ureteral stones in children is limited, and it remains unclear which patients with which stones are best suited for these strategies [13]. Surgical interventions such as ureteroscopy, percutaneous/laparoscopic/open surgeries are alternative treatment strategies, however they are invasive, associated with potential complications, expensive and require general anesthesia [1,4]. ESWL is comparably safer, however it also requires anesthesia, and pediatric ESWL centers are limited.

Understanding the natural course of ureteric stones may help develop appropriate treatment and follow-up strategies. The objective of this study is to determine what factors predict spontaneous stone passage in children with ureteral stones ≤1 cm that were treated with pain management and adequate hydration.

1. Material and methods

After obtaining local board approval, patients primarily seen by pediatricians and referred to two pediatric nephrology clinics between 2008 and 2017 were identified and records retrospectively reviewed. Patients with a single ureteric stone ≤1 cm (on a given side) were included, while patients with congenital obstructive uropathy, neurogenic bladder, vesicoureteral reflux and those with a stone diameter of >1 cm were excluded. Information on patient age, gender, initial symptom, familial history of urolithiasis, clinical and laboratory findings, imaging and treatment modalities were recorded.

Urinary ultrasonography (US) was used as the initial imaging modality while computed tomography (CT) was used when ultrasonography was inconclusive. Maximal stone diameter was measured and recorded. Cases with severe obstruction (grade 3–4 as per Society for Fetal Urology classification [14]), uncontrolled abdominal/flank pain, simultaneous febrile urinary tract infection and intractable vomiting were referred for urgent intervention (i.e. ureteroscopy). Patients who were clinically stable were treated conservatively using analgesics and adequate hydration for 2–4 weeks to try to allow spontaneous passage. These patients were evaluated weekly using plain X-ray film of the abdomen (KUB) or US. After the 2–4 week follow-up period, patients with persistent ureteric stones were referred for intervention. Patients were then divided into 2 groups after this follow up period; those who passed their stones (spontaneous passage) and those who did not pass their stones. These groups were then compared. Stone passage was defined either by obtaining the physical stone specimen or resolution of hydronephrosis with symptom resolution. For those who did not return a physical stone as evidence for passage, urinary US was repeated to determine the status of hydronephrosis. Stones collected or extracted surgically were sent for stone analysis.

A power and sample size calculation was performed with the GPower software (v.3.1.9.2, Franz Faul, Kiel University, Germany) using “spontaneous stone passage” as the main outcome variable. The expected probability of the event was taken as 57%, whereas the proportion for the alternative hypothesis was considered 40%. A Post hoc analysis demonstrated that a total sample size of 67 participants reaches a power of 80% in detecting the difference using the chi-square test with an effect size of 0.34 (medium) and an alpha error of 5%.

Data were analyzed with IBM SPSS 24.0 software. Correlation between spontaneous passage and aforementioned factors were investigated. Data were confirmed to have normal distribution using the Kolmogorov–Smirnov test, histogram inspection and coefficient of variation analyses. Categorical variables were compared using the Chi square test while continuous variables were analyzed via Student *t* test. One-way ANOVA test was used to determine if there are any statistically significant differences between the means of three or more independent (unrelated) groups. Logistic regression analysis was used to evaluate factors predictive of spontaneous stone passage. Receiver operating characteristic (ROC) curves were plotted to determine the optimal cut-off value for stone size of spontaneous passage. A p value of <0.05 or 95% confidence interval excluding 1 was considered statistically significant in all comparisons.

2. Results

A total of 70 patients (38 males, 32 females) with a median age of 4.7 years (0.2–17 years) met inclusion criteria. Family history of urolithiasis (1st or 2nd degree relatives) was present in 47 (67.1%). The most common initial symptoms were hematuria (72.9%) and abdominal/flank pain (55.7%). Of the 51 patients who reported hematuria, it was gross in 31.4% and microscopic in 68.6%. US was capable of diagnosing the ureteric stone in 47 patients (67.1%) while CT was needed in 23 (32.9%). Stone location was distal ureter in 53 (75.7%), mid ureter in 5 (7.2%) and proximal ureter in 12 (17.1%). Median stone size was 7.0 mm (3–10 mm). In terms of laterality, 37 (52.8%) patients had left sided stones, 30 (42.9%) had right sided and 3 (4.3%) had bilateral single ureteric stones. Stone analysis was available for 22 patients (calcium oxalate in 17, cystine in 4 and uric acid in 1). Table 1 summarizes demographic characteristics of patients.

Spontaneous stone passage within 2–4 weeks occurred in 40 (57.1%) patients in the whole cohort, 20 males and 20 females. Further, median time for stone passage was 8 days (3–34 days). Mean stone size in the spontaneously passed group was 5.19 ± 1.59 mm compared with 8.90 ± 1.27 mm in the negative spontaneous passage group ($p < 0.001$). Hydronephrosis was present in 29 (52.7%) patients in the spontaneous passage group while no hydronephrosis was present in 26 (47.3%) patients in the no spontaneous passage group ($p = 0.239$). There was no statistically significant difference ($p = 0.472$) between groups with respect to presence of additional kidney stones on the same side (25 patients, 61% in the spontaneous passage group vs. 16 patients, 39% in the failed spontaneous passage group).

Table 1
Initial patient characteristics.

	Frequency (n)	Percent (%)
Gender		
Male	38	54
Female	32	46
Laterality		
Left	37	52.8
Right	30	42.9
Bilateral	3	4.3
Previous stone event	11	15.7
Family history of urolithiasis	47	67.1
Presence of hydronephrosis	55	78.6
Presenting symptom		
Hematuria	51	72.9
Microscopic	35	50
Macroscopic	16	22.9
Abdominal/flank pain	39	55.7
Pyuria	24	34.3
Restlessness	14	20
Vomiting/nausea	10	14.3
Dysuria	7	10

Using the enter method, the logistic regression analysis with "Spontaneous stone passage" as the dependent and hydronephrosis (no/yes), concomitant ipsilateral kidney stone (no/yes), stone location (middle or proximal/distal), presence of hematuria (no/yes), gender (female/male), and stone size (mm) as independent variables, the model demonstrated an Cox and Snell R2 of 67.1% and an overall percentage of 94.3% in predicting spontaneous stone passage. Presence of hematuria (macroscopic and microscopic combined) and stone size were the significant predictor variables with p values 0.048 and 0.008, respectively (Table 2).

According to the ROC analysis, the most sensitive and specific stone size predicting spontaneous passage was 6.7 mm (area under the curve = 0.953; 95% CI 0.905–1.000; sensitivity 96.7%, specificity 82.5%, $p < 0.001$) (Fig. 1). Patients with stones >6.7 mm in diameter had a stone passage proportion of 17.5% (n = 7), whereas those with smaller stones had a passage ratio of 82.5% (n = 33). The difference was significant at the 0.01 level (chi-square = 45.802, $p < 0.001$).

3. Discussion

The incidence of ureteric stones in adult males is about 12% and 6% in adult females [15]. Pediatric incidence in children is relatively low; however recurrence rates are higher than adults [16,17]. Prior work has demonstrated that 73–87% of stones of any size and 54–67% of stones 5–10 mm can undergo spontaneous passage without pharmacological treatment [11,12]. Mokhless et al. reported the natural course of distal ureteric stones in 72 pediatric patients and observed that 75% of stones ≤6 mm undergo spontaneous passage [8]. Interestingly, after 6 weeks of follow-up, 68% of stones 4–6 mm in size were passed spontaneously while just 10% of stones 6–8 mm passed spontaneously. In adults, 80–90% of stones <5 mm and 61–63% of stones 5–10 mm pass spontaneously within 4 weeks [15,18]. The present study shows that 57.1% of pediatric patients spontaneously passed their stones with a mean size of 5.19 ± 1.59 mm. Additionally, ROC analysis suggests that using a size cutoff of 6.7 mm can identify which patients will need surgery and who can likely undergo successful spontaneous passage. This is in concordance with previously published series, supporting conservative treatment and the opportunity for spontaneous passage in children with ureteral stones <7 mm [9,18]. Of note, many studies regarding spontaneous passage of ureteric stones have investigated distal ureteric stones however; we studied mid and proximal ureteric stones in addition to distal ones.

The information provided in the present study allows for further evidence for selecting which clinically stable patients may be best suited for a trial of spontaneous passage. Conservative treatment for pediatric ureterolithiasis eliminates the risk of intervention related complications, which is not insignificant. A complication rate of 8.4% has been reported for ureteroscopic stone treatment in children, including ureteral perforation requiring ureteroneocystostomy [19].

Numerous studies have investigated predictive factors for spontaneous passage of ureteral stones (stone location, stone size, hydronephrosis, age and gender), with mixed results [6,8,9,21]. A retrospective analysis of 113 adult patients found that spontaneous passage was more frequent with distal ureteric stones (62% for stones 5–10 mm) [21]. Another report of 656 adult patients concluded that distal ureteric stones <6 mm had statistically significant increased spontaneous passage rate over larger stones [9]. A similar study in children revealed that distal ureteric stones <4 mm in size had a high likelihood of spontaneously passage, and neither age, nor gender, nor hydronephrosis were associated with the likelihood of spontaneous passage [8]. The present study agrees and suggests that stone size and presence of hematuria are predictive of spontaneous passage. Additionally, the current study did not find an association between stone location and passage rates, however, the small numbers of patients in each group likely underpowered this study's ability to identify any effect of stone location of spontaneous passage rates.

An alternative to watchful waiting is MET where alpha-adrenergic antagonists are commonly used to relax the ureter and facilitate stone movement. There have been 3 recent systemic reviews and meta-analysis regarding the use of MET [13,22,23], which state there is a lack of high-quality evidence that MET is beneficial in terms of stone passage in children, albeit with few side effects. However, appropriate dosage forms for children in many countries are not available, thus its use in clinical practice may be limited.

The current study shows that 67.1% of patients had ureteric stones diagnosed using US alone. This modality was also used for follow these patients. Initial diagnostic work-up for children with suspected urolithiasis is urinary US with 70% sensitivity and 100% specificity [2]. While CT scan is the gold standard, its use has increased globally in parallel with the increased incidence of pediatric urolithiasis [24]. US remains a valuable option for pediatric patients with a smaller body surface and less subcutaneous fat than adults. The current study demonstrates that US is useful for not only diagnosis but also follow-up of pediatric stone patients, minimizing radiation exposure. Thus, the ALARA (as low as reasonably achievable) principle can still be achieved with good success.

Limitations of the study include those of a retrospective study such as lack of a control group, no randomization, use of different imaging modalities and possible selection bias during initial admission. Additionally, this study was done in an area of the world with a very high stone prevalence and may not be generalizable to other countries. On the other hand, the study presents better representation of population since the clinics were in children's hospitals where a huge proportion of patients are admitted primarily rather than referred.

4. Conclusion

The present study identifies that stone size and presence of hematuria are predictive of spontaneous passage of ureteric stones in 2–4 weeks in pediatric patients. Patients with a ureteric stone size <6.7 mm can be followed conservatively with a high rate of spontaneous passage. US appears to be a useful tool for following these patients.

Acknowledgement

We would like to thank Amanda F. Saltzman, MD (Children's Hospital Colorado) for kindly reviewing the manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethics approval.

All procedures performed in the studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Table 2
Multivariate logistic regression analysis for factors to predict spontaneous stone passage.

	B	Wald	p	Exp (B)	95% CI for EXP(B) Lower	Upper
Presence of hydronephrosis	-1265	0.028	0.866	0.282	0.000	686,947.581
Additional kidney stone	0.776	0.369	0.543	2172	0.178	26.530
Stone location	2065	2200	0.138	7884	0.515	120.710
Presence of hematuria	4200	3925	**0.048**	66.664	1046	4,248.005
Gender	1638	1158	0.282	5145	0.260	101.669
Stone size (mm)	-3337	6938	**0.008**	0.036	0.003	0.426

CI: Confidence interval.

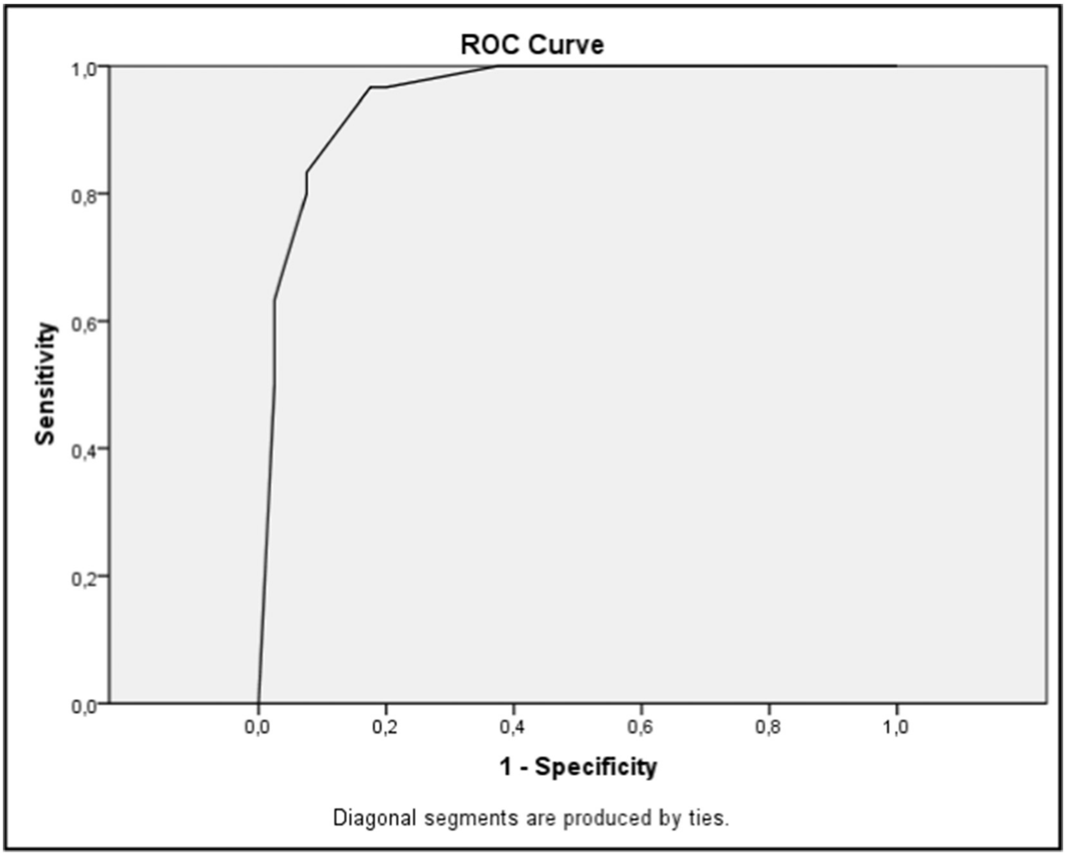

Fig. 1. Receiver operating characteristic (ROC) curve of the relationship between specificity and sensitivity for stone size of spontaneous passage.

References

[1] Van Batavia JP, Tasian GE. Clinical effectiveness in the diagnosis and acute management of pediatric nephrolithiasis. Int J Surg 2016;36:698–704 Pt D.
[2] Tasian GE, Copelovitch L. Evaluation and medical management of kidney stones in children. J Urol 2014;192(5):1329–36.
[3] Elmaci AM, Ece A, Akin F. Pediatric urolithiasis: metabolic risk factors and followup results in a Turkish region with endemic stone disease. Urolithiasis 2014;42(5):421–6.
[4] Gnessin E, Chertin L, Chertin B. Current management of paediatric urolithiasis. Pediatr Surg Int 2012;28(7):659–65.
[5] Assimos D, Krambeck A, Miller NL, et al. Surgical Management of Stones: American urological association/Endourological society guideline, PART I. J Urol 2016;196(4):1153–60.
[6] Ozcan C, Aydogdu O, Senocak C, et al. Predictive factors for spontaneous stone passage and the potential role of serum C-reactive protein in patients with 4 to 10 mm distal ureteral stones: a prospective clinical study. J Urol 2015;194(4):1009–13.
[7] Sternberg KM, Pais VM, Jr., Larson T, Han J, Hernandez N, Eisner B. Is hydronephrosis on ultrasound predictive of ureterolithiasis in patients with renal colic? J Urol 2016;196(4):1149–52.
[8] Mokhless I, Zahran AR, Youssif M, et al. Factors that predict the spontaneous passage of ureteric stones in children. Arab J Urol 2012;10(4):402–7.
[9] Tchey DU, Ha YS, Kim WT, et al. Expectant management of ureter stones: outcome and clinical factors of spontaneous passage in a single Institution's experience. Korean J Urol 2011;52(12):847–51.
[10] Jendeberg J, Geijer H, Alshamari M, et al. Size matters: the width and location of a ureteral stone accurately predict the chance of spontaneous passage. Eur Radiol 2017;27(11):4775–85.
[11] Mokhless I, Zahran AR, Youssif M, et al. Tamsulosin for the management of distal ureteral stones in children: a prospective randomized study. J Pediatr Urol 2012;8(5):544–8.
[12] Aydogdu O, Burgu B, Gucuk A, et al. Effectiveness of doxazosin in treatment of distal ureteral stones in children. J Urol 2009;182(6):2880–4.
[13] Velazquez N, Zapata D, Wang HH, et al. Medical expulsive therapy for pediatric urolithiasis: systematic review and meta-analysis. J Pediatr Urol 2015;11(6):321–7.
[14] Nguyen HT, Herndon CD, Cooper C, et al. The Society for Fetal Urology consensus statement on the evaluation and management of antenatal hydronephrosis. J Pediatr Urol 2010;6(3):212–31.
[15] Furyk JS, Chu K, Banks C, et al. Distal ureteric stones and Tamsulosin: a double-blind, placebo-controlled, randomized, multicenter trial. Ann Emerg Med 2016;67(1):86–95 e2.
[16] Tasian GE, Kabarriti AE, Kalmus A, et al. Kidney stone recurrence among children and adolescents. J Urol 2017;197(1):246–52.
[17] http://uroweb.org/guideline/paediatric-urology/.
[18] Demehri S, Steigner ML, Sodickson AD, et al. CT-based determination of maximum ureteral stone area: a predictor of spontaneous passage. AJR Am J Roentgenol 2012;198(3):603–8.
[19] Dogan HS, Onal B, Satar N, Aygun C, Piskin M, Tanriverdi O, et al. Factors affecting complication rates of ureteroscopic lithotripsy in children: Results of multiinstitutional retrospective analysis by pediatric stone disease study Group of Turkish Pediatric Urology Society. J Urol 2011;186(3):1035–40.
[21] Lee KS, Ha JS, Koo KC. Significance of neutrophil-to-lymphocyte ratio as a novel Indicator of spontaneous ureter stone passage. Yonsei Med J 2017;58(5):988–93.
[22] Glina FP, Castro PM, Monteiro GG, et al. The use of alpha-1 adrenergic blockers in children with distal ureterolithiasis: a systematic review and meta-analysis. Int Braz J Urol 2015;41(6):1049–57.
[23] Tian D, Li N, Huang W, et al. The efficacy and safety of adrenergic alpha-antagonists in treatment of distal ureteral stones in pediatric patients: a systematic review and meta-analysis. J Pediatr Surg 2017;52(2):360–5.
[24] Routh JC, Graham DA, Nelson CP. Trends in imaging and surgical management of pediatric urolithiasis at American pediatric hospitals. J Urol 2010;184(4):1816–22 Suppl.