

Analysis of factors affecting spontaneous expulsion of ureteral stones that may predict unfavorable outcomes during watchful waiting periods: What is the influence of diabetes mellitus on the ureter?

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Purpose: The aim of our study was to evaluate the association of several factors with spontaneous stone expulsion, including ureteral stone characteristics (size, location, hydronephrosis, perinephric stranding), types of medications prescribed (α -blocker, low-dose steroid), and other possible demographic and health-history factors (gender, age, serum creatinine, underlying diabetes mellitus [DM], and hypertension).

Materials and Methods: A total of 366 patients with ureteral stones were enrolled. All patients underwent watchful waiting without any invasive procedures. Initial diagnoses of ureteral stones were confirmed by computed tomography scans, which were taken at approximately 1-month intervals to check for stone expulsion. Univariate and multivariate analyses were conducted to identify significant factors that contributed to stone expulsion.

Results: Among 366 patients, 335 patients (91.5%) experienced spontaneous stone passage during a mean follow-up period of 2.95 ± 2.62 weeks. The patients were divided into two groups depending on the success of spontaneous stone passage. Univariate analyses revealed that stone location ($p=0.003$), stone size ($p=0.021$), and underlying DM ($p<0.001$) were significant predictors of stone passage. Multivariate analyses confirmed that stone size ($p=0.010$), stone location ($p=0.008$), and underlying DM ($p=0.003$) were independent predictive factors affecting stone passage.

Conclusions: Stone size, location, and underlying DM were confirmed to be significant predictive factors for spontaneous passage of ureteral stones. Urologists should consider active procedures, such as shock wave lithotripsy or ureteroscopy, rather than conservative management in patients presenting with proximally located stones, large ureteral stones, or underlying DM.

Keywords: Diabetes mellitus; Therapeutics; Ureteral calculi; Urolithiasis

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INTRODUCTION

Urinary stones are one of the most common urological problems worldwide and are actually an ancient source of serious morbidity. Urinary stone prevalence is about 1%–5% in Asia, 5%–9% in Europe, and 13% in the United States [1]. An average of 12% of people across populations has a history of urinary stones, and the overall recurrence rate is approximately 50% [2]. The recurrence interval changes over time, with 10% recurrence within 1 year, 35% within 5 years, and 50% within 10 years [3]. The annual incidence of stone formation is estimated to be 1,500 to 2,000 cases per million people [4]. Stone incidence appears to have increased continuously in recent years and might be associated with dietary changes (especially increased intake of proteins and minerals), race or ethnicity, and region of residence [5]. The age of peak incidence, in general, is between 20 and 50 years [6].

Current treatment options for ureteral stones include conservative management as well as active procedures, such as shock wave lithotripsy (SWL) and ureteroscopy (URS). As a result of instrumental and technical advances over the past few decades, the success rates of stone-related procedures have increased while complication risks have decreased. Despite the benefits of active interventions, however, they are expensive and still pose a greater than minimal risk [7,8]. Perioperative complications that lead to fatalities can still occur, albeit rarely.

In a meta-analysis of previous studies, most ureteral stones located in the distal ureter, approximately 68% of ureteral stones ≤ 5 mm and 47% of stones between 5 and 10 mm, were expelled spontaneously [9]. Not all ureteral stones require aggressive intervention; distal stones less than 5 mm in size have a spontaneous passage rate of 71% to 98% [6]. Stone size and location are important to consider when deciding whether to take a watchful management strategy. Also, painkillers are required for patients with intolerable pain caused by stone passage. As long as the patient is not suffering from stone-related symptoms, including unmanageable pain, conservative management (i.e., watchful waiting) is an appealing, low-cost approach. Some medications, such as α -blockers, calcium-channel blockers, furosemide, and corticosteroids, have also been found to be effective therapies that promote stone expulsion. A recent meta-analysis found a 65% or better stone expulsion rate among patients taking either α -blockers or calcium-channel blockers [10].

The purpose of our study was to identify significant factors that predict successful stone passage without the use

of invasive procedures, such as SWL or URS. Knowing the factors that play a role in the clinical outcome of watchful waiting for ureteral stones would allow us to select effective treatment options while lowering the risk of complications.

MATERIALS AND METHODS

1. Study population

This study was conducted at the Department of Urology, Kyung Hee University School of Medicine, between March 2011 and February 2014. Approval was obtained from the relevant Institutional Review Board (IRB No. 2014-10-008). The electronic medical records of patients who had been diagnosed with ureteral stones were reviewed retrospectively. Criteria for study enrollment included patients who had been diagnosed with a ureteral stone by computed tomography (CT) scan, who had received conservative management for small stones (<4 mm), and who had not received enhanced therapies such as SWL or URS despite large sized stones (≥ 4 mm). Only patients with a single unilateral ureteral stone regardless of size were included in the study. Exclusion criteria were pregnancy, multiple ureteral stones, urethral or ureteral stricture, history of stroke, genitourinary tract anomaly, single kidney, and urinary tract infection. The factors we measured as having potential effects on the clinical outcome of conservatively managed ureteral stones were stone size, stone location, the degree of hydronephrosis measured by CT, presence of perinephric stranding, medication use (e.g., α -blocker and/or corticosteroid), gender, age, serum creatinine level, and underlying diabetes mellitus (DM) or hypertension (HTN). The presence of DM was diagnosed by a DM specialist if the standard diagnostic criteria were met. Mean glycated hemoglobin (HbA1c) level was also investigated as a potential factor and was analyzed among patients with DM. It was calculated by checking HbA1c every 3 months for up to 2 years.

2. Study protocol

All inpatient and outpatient cases ($n=366$) presenting to our department with a ureteral stone diagnosis were included in this study. The initial diagnosis was confirmed via CT and laboratory studies, including urine analysis with microscopic examination, urine culture, complete blood count with differential, serum blood urea nitrogen, creatinine, calcium, and uric acid. The patients were divided into two groups: a “no passage” group that had failed to spontaneously pass their stones during follow-up and a “passage” group that successfully passed their stones. We confirmed the

success or failure of stone expulsion through CT scans taken at approximately 1-month intervals. For the sake of accuracy, we excluded patients who did not have any stone-related symptoms and therefore refused follow-up imaging study. All patients in both groups received individually tailored conservative treatment, which is described below. Some patients (n=145) took no medication, whereas other patients (n=221) took a daily dose of 0.2 mg of tamsulosin, either with or without 5 mg of a corticosteroid; patients who complained of colicky pain during follow-up received painkillers such as tramadol or ketorolac. Tamsulosin was prescribed regardless of comorbidity such as HTN or DM.

3. Statistical analyses

IBM SPSS Statistics ver. 20.0 (IBM Co., Armonk, NY, USA) was used for all statistical analyses of stone-passage factors. Two-tailed t-tests and chi-square tests were used to identify significant differences between the no-passage group and the passage group. We also fit a linear logistic regression model. Two-tailed t-test results and univariate and multivariate analyses with p<0.05 were considered statistically significant.

RESULTS

The mean age of the 366 patients (215 men [58.7%], 151 women [41.3%]) included in this study was 47.05±14.61 years. Forty-six patients (12.6%) had HTN and 26 patients (7.1%) had DM. Spontaneous stone expulsion was observed in 335 of 366 patients (91.5%). No significant differences were found between the no-passage group and the passage group with respect to age (p=0.359), gender (p=0.488), stone side (p=0.435), serum creatinine (p=0.837), degree of hydronephrosis (p=0.237), perinephric stranding (p=0.660), α-blocker use (p=0.659) and/or corticosteroid intake (p=0.082), or underlying HTN (p=0.515). In the univariate analysis, the factors that significantly predicted stone-expulsion failure include large stone size (p=0.021), proximal stone location (p=0.003), and underlying DM (p<0.001) (Table 1). Six patients (23.1%) among 26 patients with DM failed stone expulsion. Although steroid medication showed a trend toward affecting stone passage, this was not significant (p=0.082).

In our multivariate linear logistic regression models, stone size (p=0.010; odds ratio [OR], 2.822), stone location (p=0.008; OR, 0.588), and underlying DM (p=0.003; OR, 4.621) remained independent factors predicting stone passage

Table 1. Baseline characteristics of the study population

Characteristic	No passage group (n=31)	Passage group (n=335)	p-value
Age (y)	49.35±12.79	46.83±14.76	0.359
Sex			0.488
Male	20 (64.5)	195 (58.2)	
Female	11 (35.5)	140 (41.8)	
Side			0.435
Left	18 (58.1)	170 (50.7)	
Right	13 (41.9)	165 (49.3)	
Stone size (mm)	4.29±1.45	3.68±1.41	0.021
Stone location			0.003
Proximal ureter	15 (48.4)	85 (25.4)	
Mid ureter	2 (6.5)	12 (3.6)	
Distal ureter	14 (45.1)	238 (71)	
Hydronephrosis			0.237
None	0 (0)	27 (8.1)	
Yes	31 (100)	308 (91.9)	
Perinephric stranding	15 (48.4)	175 (52.2)	0.660
α-Blocker	20 (64.5)	201 (60)	0.659
Corticosteroid (5 mg/d)	18 (58.1)	140 (39.4)	0.082
Serum creatinine (mg/dL)	0.95±0.29	0.97±0.31	0.837
Hypertension	5 (16.1)	41 (12.2)	0.515
Diabetes mellitus	7 (22.6)	19 (5.7)	<0.001
HbA1c (n=23)	7.297±0.941 (n=6)	7.044±1.264 (n=17)	-

Values are presented as mean±standard deviation or number (%). HbA1c, glycosylated hemoglobin.

Table 2. Characteristics of the study population and multivariate logistic regression outcomes

Variable	Odds ratio (95% CI)	p-value
Stone size (mm)		
<4/≥4	2.822 (1.280–6.220)	0.010
Stone location		
Proximal/mid/distal	0.588 (0.396–0.873)	0.008
Diabetes mellitus		
Yes/no	4.621 (1.693–12.610)	0.003

CI, confidence interval.

failure (Table 2). Although underlying DM was shown to be a determining factor, mean HbA1c levels were not significantly different between the two groups ($p=0.213$; OR, 2.25). No side effects that required cessation of treatment were encountered.

DISCUSSION

Urinary stones are the third most common disease of the genitourinary tract, following urinary tract infections and prostatic problems. The annual incidence of urinary stones in Korea is estimated to be 457 per 100,000 in the general population [11]. Urinary stones indicate various metabolic disturbances resulting from interactions between multiple pathological factors. Stone disease is a particularly irritating complication because of its acute onset and association with severe colicky pain. Having a ureteral stone for a prolonged time may result in serious complications such as acute pyelonephritis or irreversible deterioration of renal function. After providing an initial diagnosis of ureteral stones, physicians should quickly devise a reasonable management plan for their patients to improve prognosis and minimize potential risks. Several treatment options are available for ureteral stones, including watchful waiting, medical expulsive therapy, SWL, and URS. SWL and URS have higher success rates, but these procedures can also cause serious complications such as hematuria, hematoma, ureteral or urethral injury, and anesthetic problems. Watchful waiting with or without medication can be a desirable option in select patients. In patients with tiny ureteral stones located in the distal ureter, most urologists can choose to provide conservative management to allow for spontaneous stone expulsion. Although the clinical course of stone disease may be accompanied by severe colicky pain, if the pain is tolerable and controllable, continued waiting with supportive painkillers can be effective. The time interval suggested for spontaneous expulsion is 4 weeks according to the European Association of Urology guidelines.

Previous studies have verified the clinical prognosis and advantages of conservative management for ureteral stones. Among ureteral stones that were ≤ 5 mm, 68% passed spontaneously, whereas 47% of stones sized 5 to 10 mm were expelled spontaneously [9]. Another study found that distal ureteral stones < 5 mm have a spontaneous passage rate of 71% to 98% [6]. Nevertheless, waiting for spontaneous stone expulsion does not always result in an ideal outcome and the colicky pain can become recurrent. Furthermore, delayed intervention sometimes results in catastrophic events, such as complicated urosepsis.

Spontaneous stone passage can be unpredictable in the case of ureteral edema with or without spasm, which is assumed to delay stone passage. Medication has been developed to target that aspect of stone disease and is considered to improve stone expulsion [10]. Alpha-blockers have been found to be an effective method to promote stone expulsion, especially in cases with a distal ureteral stone. Most of our patient group took 0.2 mg of tamsulosin daily for medical expulsive therapy. Tamsulosin is one of the most used $\alpha 1$ -blockers for the management of ureteral stones, and it has equal affinity for $\alpha 1a$ and $\alpha 1d$ receptors [12]. The $\alpha 1d$ receptor is the most dominant receptor in the ureter and is especially concentrated in the distal portion [13]. Administration of α -blockers is established to help spontaneous stone expulsion, but the effect is not statistically significant; this may be due to insufficient dosages of tamsulosin. The lack of data regarding patient outcomes after receiving a higher daily dose of tamsulosin (e.g., 0.4 mg) is one limitation of our study. Furthermore, the various length of the follow-up period may have altered the clinical correlation. Previous studies have reported that stones were expelled in the first 10 days of medical therapy with a low incidence of permanent kidney damage [14].

Ureteral peristalsis plays an important role in urine ejection from the kidneys to the bladder through the ureter. It is mediated by involuntary muscular contractions of the ureteral wall. Functional impairment of ureteral peristalsis not only induces stone formation, but also interrupts stone expulsion. Several studies have established the specific circumstances that may reduce ureteral peristalsis [15,16]. In addition, a clinical trial was conducted that used an animal model to explore whether ureteral peristalsis could be modulated with medications, including atropine, carbachol, and diuretics [17].

DM is one of several metabolic diseases that result from consistently elevated blood glucose levels over a long period of time. DM can cause mild to life-threatening complications despite great efforts to control it. Lower urinary tract

symptoms that originate from DM are found in over 80% of all patients [18]. Typical urologic complications of diabetes that result from DM-related nerve damage include urinary tract infection, neurogenic bladder, and erectile dysfunction; however, little is known about the clinical course or pathophysiology of these complications. The contractile activity of ureteral smooth muscle is controlled by the autonomic nervous system [19]. Peripheral neuropathy originating from systemic disease is one possible explanation and DM is a common cause of neuropathy. About 60% to 70% of patients with DM have some degree of nervous system damage. However, no one has clearly identified whether DM has a significant influence on the ureter, and, if so, what the mechanism is.

Recent studies have shown that tight glucose control in DM patients might reduce macrovascular and microvascular complications [20]. Vascular smooth muscle cell dysfunction related to high glucose is a key diabetic complication [21]. High glucose levels induce vascular endothelial injury and increase levels of glucose transporter-1, which is involved in vascular smooth muscle cell proliferation [22]. This can ultimately cause hyperproliferation of vascular smooth muscle [21]. The hyperproliferation of vascular smooth muscle leads to undesirable results, such as vascular malfunction, stenosis, and atherosclerosis.

Serum HbA1c is an index of average glucose levels over a relatively short time period (e.g., a few months); it is commonly used to estimate the effectiveness of DM management. Uncontrolled DM increases HbA1c levels and is associated with a higher risk of complications, including nephropathy, vasculopathy, and neuropathy. The mean HbA1c in the no-passage group ($n=6$, 7.297 ± 0.941) was slightly higher than in the passage group ($n=17$, 7.044 ± 1.264), but the difference between the two groups was not significant ($p=0.213$). The small numbers in our study groups may have weakened our power to identify a meaningful correlation between HbA1c levels and stone expulsion. A large-scale, prospective study may be helpful in establishing the potential prognostic role of HbA1c.

Our study had a few limitations, as mentioned previously. To compensate for these shortcomings, a follow-up prospective, large-scale study is needed to confirm our findings about the potential risk of DM on ureteral stone management. We can confidently conclude that stone size and location are the most important factors for predicting spontaneous stone passage [23]. However, checking for the presence of DM might also be helpful in predicting ureteral stone prognosis. In short, stone size, location, and underlying DM can be used as determining factors in

treatment decisions regarding invasive procedures for stone management.

CONCLUSIONS

Previous studies have demonstrated some advantages of conservative management in stone expulsion. This noninvasive watchful waiting may also reduce the cost of treatment and prevent unnecessary surgeries in select patients. However, on the basis of our data analyses, we suggest that large, proximal stones in patients with underlying DM should be considered candidates for more invasive treatment, such as SWL or URS.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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