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

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Purpose: We investigated possible predictive factors for spontaneous stone passage and the potential role of serum C-reactive protein and white blood count in patients with 4 to 10 mm distal ureteral stones.

Materials and Methods: A total of 251 patients who presented with renal colic secondary to distal ureteral stone were included in study. Patients were grouped according to spontaneous stone passage. Serum C-reactive protein, white blood count and other possible factors were investigated for their potential predictive value for spontaneous stone passage at a followup of 5 weeks. Potential predictive factors for spontaneous stone passage were evaluated with univariate and multivariate analyses. ROC curve analysis was performed to find an optimal cutoff value for serum C-reactive protein according to spontaneous stone passage. Statistical significance was considered at $p < 0.05$.

Results: Spontaneous stone passage was observed in 135 patients (53.8%) in group 1 while 116 (46.2%) in group 2 did not expel the stone spontaneously. Median stone size was 5.7 mm. Stone size, serum C-reactive protein and white blood count were significantly higher in group 2 than in group 1. The number of patients with hydronephrosis and the number with spontaneous stone passage history were significantly lower in group 2 compared to group 1. The cutoff value of serum C-reactive protein provided by ROC analysis was 0.506 mg/l. Time to spontaneous stone passage was significantly higher in patients with serum C-reactive protein above the threshold and in patients with ureteral stones greater than 6 mm.

Conclusions: Stone size, previous spontaneous passage, hydronephrosis, serum C-reactive protein and white blood count can be used to predict spontaneous stone passage in patients with 4 to 10 mm distal ureteral stones. A serum C-reactive protein level of 0.506 mg/l can serve as a cutoff value to predict spontaneous stone passage.

Key Words: ureter, calculi, C-reactive protein, leukocyte count, prognosis

Abbreviations and Acronyms

BMI = body mass index
CRP = C-reactive protein
CT = computerized tomography
ESWL = extracorporeal shock wave lithotripsy
MET = medical expulsive therapy
SSP = spontaneous stone passage
WBC = white blood count

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Ureteral stone disease is responsible for 20% of urolithiasis cases and has a prevelance rate of 3% to 5%.[1–3] Renal colic due to ureteral stones may negatively affect patient quality of life and routine daily activities, causing significant pain and discomfort.[1,4] Management of renal colic due

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to ureteral stones is controversial. Therapeutic alternatives include conservative treatment, ESWL and ureteroscopy.[1]

MET is widely used as a part of conservative management to promote SSP in patients with distal ureteral stones.[3] Although conservative management is simple and cost-effective, it may possibly cause some problems, including renal function deterioration, urosepsis and continuing renal colic pain.[1,3,5,6] ESWL and ureteroscopy are effective and safe procedures that may be preferred in patients with ureteral stones but even they are not without some complications.[1,3] Furthermore, ureteroscopy and ESWL might possibly cause additional cost and overtreatment in patients with ureteral stones that would most likely pass spontaneously.[1,5,7]

Factors that can be used to predict SSP include stone diameter, duration of pain, pyuria and hydronephrosis.[2,3,8,9] Previously the incidence of SSP for distal ureteral stones was reported to be 71% to 98% for stones 5 mm or less and 25% to 51% for stones greater than 5 mm.[3,8] CRP is an acute phase protein that increases as a result of inflammation.[2,3] The inflammatory response due to ureteral stone can cause an increase in the serum CRP level. Serum CRP was previously used to interpret some urological diseases, including pyelonephritis, vesicoureteral reflux, urinary tract infection and ureteral stones.[3,10–12]

Proper selection of ureteral stone patients who would most likely benefit from conservative treatment, ESWL or ureteroscopy is critical but still controversial. In the current prospective study we aimed to investigate possible predictive factors for SSP and the potential role of serum CRP and WBC in patients with 4 to 10 mm distal ureteral stones.

MATERIALS AND METHODS

The study was approved by the institutional ethics committee. Initially 339 patients admitted to the emergency department or urology outpatient clinic from November 2013 to January 2015 for acute renal colic secondary to distal ureteral stone were included in study. During followup 88 patients were excluded from study, including 12 who could not continue MET due to side effects, 6 with acute pyelonephritis, 11 who required nephrostomy catheter or Double-J® stent insertion, 36 who did not complete followup and 23 who underwent ureteroscopy before 5 weeks due to renal function deterioration or pain despite analgesia use.

The study was designed to be prospective. All patients had a solitary 4 to 10 mm distal ureteral stone and patients older than 17 years were eligible for inclusion in the study. All patients were asked to drink 2 L of water daily. They used an α-blocker and a nonsteroidal anti-inflammatory drug for MET and pain relief. Stone size was noted as the longest diameter. Age, gender, cigarette smoking history, BMI, side of the stone, serum WBC, serum CRP measured before nonsteroidal anti-inflammatory drug use, previous SSP and previous ureteroscopy history were noted. Total blood count, urinalysis, serum CRP and renal function tests were done at presentation. Stone identification was performed by plain abdominal film of the kidneys, ureters and bladder, urinary system ultrasound and noncontrast CT. The degree of renal dilatation on noncontrast CT was noted in all patients according to the SFU (Society for Fetal Urology) Hydronephrosis Classification System.

Patients were followed weekly during 5 weeks with plain abdominal film of the kidneys, ureters and bladder, and ultrasound and noncontrast CT if required for SSP by the same radiologist, who was experienced with urinary system imaging. Patients who failed to expel the ureteral stone spontaneously within 5 weeks of followup underwent ureteroscopy.

All patients were informed about the study and proper treatment alternatives. Patients who required early intervention due to impaired renal function, solitary kidney, severe renal colic pain resistant to medical treatment or hydronephrosis grade 3 or greater and those who preferred active stone removal were not included in analysis. Exclusion criteria were a history of renal colic more than 2 hours before presentation, fever 38C, urinary tract infection, recently diagnosed or active infection of another origin, multiple ureteral stones, chronic renal failure, congenital urinary anomalies, previous open or endoscopic ureteral surgery, malignancy, inflammatory disease, liver failure and pregnancy. Patients receiving medications that could potentially affect serum CRP and WBC, including contraceptives and glucocorticoids, and patients who required insertion of a Double-J stent or percutaneous nephrostomy catheter were also excluded from study.

Patients were grouped according to spontaneous stone passage. Descriptive statistics are presented as the median and range, and mean $\pm$ SD. Patients who did and did not expel the stone spontaneously were compared by age, gender, stone size, degree of hydronephrosis, side of the stone, smoking history, BMI, previous spontaneous stone passage, and serum WBC and CRP on univariate analysis. The Mann-Whitney U test was used to compare the means of numerical variables without a normal distribution. To define risk factors for the outcome variable (spontaneous stone passage) multivariable logistic regression analysis was done. Prior to multivariable logistic regression analysis of the association of each independent variable (age, gender, stone size, CRP, previous SSP and hydronephrosis grade) with the outcome variables a univariate estimate was determined by logistic regression analysis. The OR and 95% CI are shown.

Two groups were compared for the number of patients who had serum CRP greater and less than the cutoff value using the chi-square test. ROC curve analysis was performed to find an optimal cutoff value for serum CRP according to SSP. The cutoff was determined using the Youden index and the maximum value of the index served as a criterion to select the optimum cutoff point. The chi-square test was applied to compare time to stone passage in association with the CRP level and stone size in patients

who spontaneously expelled the stone. Patients were further grouped as younger than 60 years, or 60 years old or older and compared for SSP rates by the chi-square test. SPSS®, version 11.5 was used for statistical analyses with $p < 0.05$ considered statistically significant.

RESULTS

SSP was observed in 135 group 1 patients (53.8%) while 116 (46.2%) in group 2 did not expel the stone spontaneously. Median stone size was 5.7 mm (range 4 to 9.80). Table 1 shows patient characteristics in the 2 groups. Stone size, serum CRP and serum WBC were significantly higher in group 2 compared to group 1 ($p < 0.001$). The number of patients with hydronephrosis and the number with a SSP history were significantly lower in group 2 than in group 1 ($p < 0.001$).

ROC analysis resulted in an AUC of 0.723 for serum CRP ($p < 0.001$, see figure). The cutoff value for serum CRP provided by the analysis was 0.506 mg/l. SSP was observed in 39 patients (28.9%) with CRP greater than 0.506 mg/l and in 96 (71.1%) with CRP below 0.506 mg/l. Median time to SSP was 13 (range 3 to 31) and 17 days (range 5 to 34) in patients with CRP 0.506 mg/l or less and greater than 0.506, respectively ($p = 0.028$). Median time to SSP was 12 (range 3 to 34) and 25 days (range 10 to 31) in patients with a stone 6 mm or less and greater than 6 mm, respectively ($p = 0.001$). Time to SSP was significantly higher in patients with serum CRP above the threshold value and in patients with ureteral stones greater than 6 mm.

Table 2 lists the outcomes of multivariate analysis for potential factors that could predict SSP. On multivariate analysis increased age, greater stone size, increased serum CRP, a negative previous SSP history and hydronephrosis less than grade 2 were negative predictive factors for SSP (table 2). SSP was observed in 128 patients younger than 60 years and in 7 who were 60 years old or older. The SSP rate was significantly decreased in patients 60 years old or older ($p < 0.001$).

DISCUSSION

Colic pain due to ureteral stones represents one of the most common urological emergencies.[3,13] There is controversy regarding the further optimal treatment of patients with ureteral stones following the initial treatment of ureteral colic pain.[1–3] Options for managing ureteral stones include conservative treatment and active stone removal with minimal invasive techniques, including ESWL and ureteroscopy.[1,14] Ureteroscopy is the most preferred invasive method for distal ureteral stones with success rates between 57% and 92%.[1,7] Despite high success rates ureteroscopy is not complication free and it is more expensive than conservative management.[1,2,15]

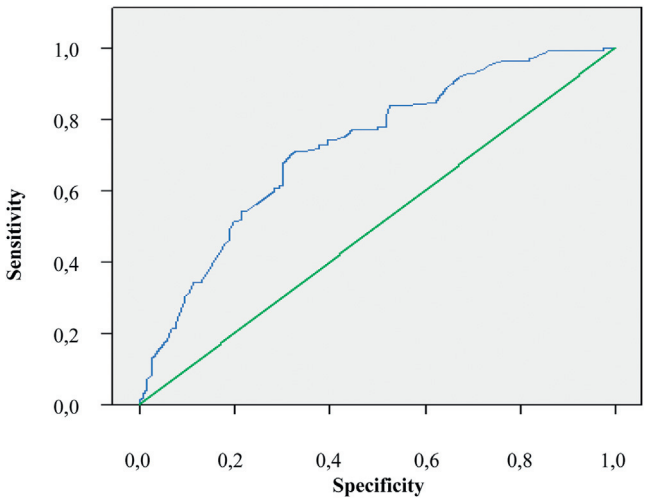
Most distal ureteral stones, particularly those smaller than 5 to 6 mm, can potentially pass spontaneously.[1,7] Therefore, in appropriate cases conservative management represents a simple and cost-effective option. However, patient selection criteria for conservative management are not clear and waiting without intervention may possibly cause serious complications, including renal function deterioration and urosepsis.[1,5,6] In addition, failure of conservative management may cause higher cost compared to early stone removal.[3,16]

Selection between invasive techniques and conservative management is one of the major dilemmas in urology practice. Thus, several groups have focused on possible predictive factors for spontaneous passage in patients with ureteral stones.[1–3,6,7,17] Previous studies investigated the potential role of stone size and location to predict SSP.[6,7,17,18] Several studies showed high rates of spontaneous passage for distal ureteral stones smaller than 5 mm.[1,17,18] In our series all patients had distal ureteral stones and stone size was a significant predictor of SSP on univariate analysis,

Table 1. *Patient characteristics*

	Spontaneous Passage	No Spontaneous Passage	p Value
No. pts	135	116	
Median age (range)	37 (18–66)	42 (18–71)	0.017*
No. male/female	75/60	66/50	0.831
Stone:			
Mean ± SD size (mm)	5 ± 1.38	6.15 ± 1.77	<0.001*
No. lt/rt	62/73	46/70	0.317
No. hydronephrosis:			<0.001*
0	113	57	
1/2	22	59	
Median mg/l CRP (range)	0.34 (0.01–4.64)	0.92 (0.10–7.19)	<0.001*
Median WBC/μl (range)	6,600 (7,200–14,500)	9,550 (5,100–18,300)	<0.001*
No. spontaneous passage history (%)	49 (36.3)	22 (19.0)	<0.001*
Mean ± SD BMI (kg/m^2)	26.1 ± 3.4	26.8 ± 3.1	0.578
No. smoking (%)	38 (28.1)	29 (25.0)	0.574

* Statistically significant ($p < 0.05$).



ROC analysis of serum CRP (AUC 0.723, p <0.001)

which was confirmed by multivariate analysis. We also found that time to SSP was statistically greater in patients with ureteral stones larger than 6 mm.

Several predictive factors other than stone size and location have been widely examined in previous studies.[1–3] In a recent series increased WBC and neutrophil count significantly predicted SSP.[1] In contrast, Park et al found that the passage rate of ureteral stones in patients with a higher neutrophil count was lower than in patients with a normal neutrophil count.[2] In the current study we found that WBC was significantly higher in patients who did not expel the stone spontaneously. We think that obstruction by an impacted stone, which is more likely not to pass spontaneously, may potentially cause an increase in serum WBC due to inflammatory responses.

Previous SSP history and hydronephrosis were also predictive factors for stone passage on univariate and multivariate analysis. Although age was not statistically different between the groups on univariate analysis, multivariate analysis suggested that age is a predictive factor for spontaneous stone passage. In addition, the SSP rate was significantly lower in patients older than 60 years. In a previous study esophageal motility decreased due to possible deterioration in neuromuscular activity in older patients.[19] We think that advanced age may negatively effect ureteral peristalsis by a mechanism similar to that of esophageal peristalsis. Further studies of the possible relation between age and ureteral peristalsis are required. In addition, we think that these findings may be due to the negative effects of a more sedentary lifestyle and possible decrease in ureteral peristalsis with increased age.

Table 2. *Multivariable analysis of potential factors that can predict SSP*

	OR (95% CI)	p Value
Age	0.958 (0.935–0.981)	0.001*
Gender	1.224 (0.659–2.274)	0.523
Stone size	0.632 (0.514–0.714)	0.001*
CRP	0.473 (0.320–0.699)	0.001*
Previous SSP history	2.287 (1.125–4.650)	0.022*
Hydronephrosis	4.481 (2.239–8.639)	0.001*

* Statistically significant at p <0.05.

Serum CRP is another marker that has been investigated in some recent series as a potential predictive factor for SSP in patients with ureteral stones.[2,3] In a recent retrospective study Park et al examined the relationship of the spontaneous passage rate of ureteral stones smaller than 8 mm with the CRP level and the neutrophil count.[2] They concluded that measuring serum CRP and neutrophil percentages in patients with small ureteral stones (less than 8 mm) is useful to predict whether the stone will be spontaneously passed. In another study Aldaqadossi assessed the usefulness of CRP to assist in making a decision for early active removal or observation of ureteral stones.[3] In that series all patients were followed for 4 weeks for spontaneous passage. Aldaqadossi concluded that the success of MET for managing small distal ureteral stones could be predicted by the serum CRP level.

A meta-analysis of 328 patients harboring ureteral stones less than 10 mm investigated the likelihood of ureteral stone passage.[20] Average time to pass a ureteral stone between 4 and 6 mm was 39 days. In our study all patients underwent MET and were followed weekly during 35 days for spontaneous stone passage. In the current series univariate analysis showed that serum CRP was significantly higher in patients who did not expel the ureteral stone spontaneously. CRP was also a significant predictive factor for spontaneous passage on multivariate analysis. The threshold value for serum CRP provided by ROC analysis was 0.506 mg/l and the spontaneous passage rate was significantly higher in patients with serum CRP 0.506 mg/l or less. We also found that time to SSP was statistically less in patients with a serum CRP level of 0.506 mg/l or less compared to a level greater than 0.506 mg/l.

Serum CRP is a nonspecific marker of systemic inflammation that may reflect the severity of inflammatory processes.[3] In a previous study Yamaguchi et al reported that impacted stones induce ureteral wall inflammation.[21] Although pathophysiology at the ureteral level during stone passage is not clear, obstruction by an impacted ureteral stone may possibly trigger ureteral inflammation and edema, interfering with spontaneous passage.[1,2] In addition, obstruction by an impacted stone may potentially cause an increase in serum WBC and CRP due to inflammatory responses.[2] To our knowledge the current study represents the first

prospective clinical trial of possible predictive factors for SSP and the potential role of serum CRP and WBC in patients with 4 to 10 mm distal ureteral stones within a 35-day followup.

The current study has some limitations. Our patients used different α-blockers for MET and further studies with standardized MET are required. Since our hospital is a referral institution, fewer patients who come from peripheral regions are referred to our hospital in whom excretory urogram was already performed. We mostly did not perform noncontrast CT in these few patients if the current excretory urogram revealed the stone and dilatation. However, the use of different imaging methods might possibly cause bias.

Another limitation is the exclusion of patients who had some conditions possibly associated with increased serum CRP and WBC count. Further studies are required to investigate the predictive role of CRP and WBC for SSP in patients with conditions that can cause an increase in inflammatory markers, including CRP and WBC. Given the observational nature of the current study, we acknowledge the possibility of unknown or unmeasured confounders. Lastly, although we asked all patients to drink 2 L of water daily, it was not possible to standardize hydration.

CONCLUSIONS

Stone size, previous SSP history, hydronephrosis, serum CRP and WBC count are potential factors that can be used to predict SSP in patients with 4 to 10 mm distal ureteral stones. Patients with serum CRP 0.506 mg/l or less have a high SSP rate and can be treated conservatively.

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