

Endourology/Urolithiasis

Relationship Between Spontaneous Passage Rates of Ureteral Stones Less Than 8 mm and Serum C-Reactive Protein Levels and Neutrophil Percentages

Chang Hyun Park, Ji Yong Ha, Choal Hee Park, Chun Il Kim, Kwang Se Kim, Byung Hoon Kim

Department of Urology, Keimyung University School of Medicine, Daegu, Korea

Purpose: A ureter obstruction caused by a ureteral stone results in inflammatory changes in the proximal submucosal layer and prevents the spontaneous passage of the ureteral stone. Accordingly, we analyzed the relationship between the spontaneous passage rates of ureteral stones less than 8 mm in size and serum C-reactive protein (CRP) levels and neutrophil percentages.

Materials and Methods: A total of 187 patients who were diagnosed with ureteral stones less than 8 mm in size and were managed consecutively at Keimyung University Dongsan Medical Center from January 2001 to January 2011 were retrospectively analyzed. Ureteral stone removal was defined as no ureteral stone shown in an imaging test without any treatment for 8 weeks after diagnosis. The patients were divided into three groups according to the levels of serum CRP and into two groups according to neutrophil percentage. The associations between these factors and ureteral stone passage rates were then examined.

Results: The ureteral stone passage rates of the low serum CRP level group, the medium serum CRP level group, and the high serum CRP level group were 94.1% (159/169), 70% (7/10), and 50.0% (4/8), respectively. The passage rates of ureteral stones in the group with a normal neutrophil percentage and in the group with a higher neutrophil percentage were 94.5% (121/128) and 83.1% (49/59), respectively (p=0.011).

Conclusions: Measuring serum CRP levels and neutrophil percentages in patients with small ureteral stones of less than 8 mm is useful in predicting whether the stone will be spontaneously passed. When the serum CRP level and neutrophil percentage of a patient are high, aggressive treatment such as extracorporeal shock wave lithotripsy should be considered.

Keywords: C-reactive protein; Neutrophil; Ureterolithiasis

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Article History:

received 20 March, 2013

accepted 2 July, 2013

Corresponding Author:

Byoung Hoon Kim
Department of Urology,
Keimyung University Dongsan
Medical Center, 56 Dalseong-ro,
Jung-gu, Daegu 700-712, Korea
TEL: +82-53-250-7646
FAX: +82-53-250-7643
E-mail: blackporori@dsmc.or.kr

INTRODUCTION

A ureteral stone is a relatively common condition from which 1% of the population suffers and whose prevalence ranges from 3% to 5% [1]. Diverse treatment methods exist, including conservative management, extracorporeal shock wave lithotripsy, endoscopic removal, and percutaneous treatment. It is not clearly established in which cases conservative management should be applied or in which cases

an invasive approach is necessary. In the selection of a treatment method, the complications of each method, patient preference, and treatment period should be considered, and treatment success rates are also an important factor. In particular, the spontaneous passage rate of a ureteral stone is high in a patient with a small ureteral stone, and whether the selection of an invasive approach at an early stage is a cost-efficient treatment method may be disputed. If predictive factors could be identified for wheth-

er the spontaneous passage of a ureteral stone can be expected, it would be helpful for selecting a treatment method.

Serum C-reactive protein (CRP) levels and neutrophil percentages are factors that increase as a result of inflammatory responses and are clinically used as indexes of the degree of inflammation. Ureter obstruction caused by a ureteral stone triggers inflammatory change in the proximal submucosal layer and prevents removal of the stone. We aimed to examine how increases in serum CRP levels and neutrophil percentages differ in relation to success rates of spontaneous passage during conservative management. To look at the effects of the degree of inflammation in the ureter on the treatment of a ureteral stone less than 8 mm, we analyzed the relationship between spontaneous passage rates of ureteral stones and serum CRP levels and neutrophil percentages.

MATERIALS AND METHODS

1. Patients and methods

The medical records of patients who were diagnosed with a ureteral stone less than 8 mm in size and who received conservative treatment were retrospectively analyzed. Those who had acute or chronic infections, a single kidney, or multiple ureteral stones were excluded. Those who complained of pain that was not improved by painkiller injection or fluid therapy during conservative management and therefore received an intervention or a surgical treatment and those who were not under follow-up observation were also excluded. The number of patients included was 187 and their average age was 47.0 years (range, 26 to 71 years). All patients underwent nonenhanced abdominal computed tomography and X-ray examination of the kidney-ureter-bladder, and their CRP levels and neutrophil rates were measured. Within 8 weeks, an imaging test was conducted again to verify whether the ureteral stone had been passed. After diagnosis, the patients were orally administered 10 mg ketorolac tromethamine (Tarasyn, Roche Pharma, Basel, Switzerland) and 2 capsules of terpene mixture (Rowatinex, Pharmbio Korea, Seoul, Korea) three times a day as a conservative management for pain relief. Those who visited Keimyung University Dongsan Medical Center or were delivered to the emergency room were intravenously administered 25 mg pethidine hydrochloride (Pethidine HCl, Jeil Pharma, Seoul, Korea) once and those who complained of continuous pain were administered the same dose of the pain killer once more [2]. Natural passage of a ureteral stone was defined as no stone seen on an imaging test within 8 weeks after the diagnosis of a ureteral stone and the start of conservative management.

The spontaneous passage rates of patient groups formed according to serum CRP levels and neutrophil percentages were compared. The patients were divided into three groups with serum CRP levels of 0–4.9 mg/dL, 5.0–9.9 mg/dL, and over 10 mg/dL; the number of patients in each group was 169 (90.5%), 10 (5.3%), and 8 (4.2%), respec-

tively. The patients were also divided into a group with normal neutrophil percentages of 38–74% and a group with higher neutrophil percentages; the number of patients in the two groups was 128 (68.4%) and 59 (31.6%), respectively.

2. Statistical analysis

Patient characteristics were investigated by use of Student t-test, chi-square test, and linear by linear test. The association between the above factors and ureteral stone removal rates was investigated. Multivariate logistic regression analysis was conducted by using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

RESULTS

The number of patients in whom ureteral stones passed spontaneously was 170 of the total 187 cases (90.9%). There were no significant differences in age, gender, or size of ureteral stones between the groups. The only significant difference was in stone location (Table 1). In relation to serum CRP levels, the number of patients whose ureteral stones were naturally passed was 159 of 169 (94.1%) in the group with serum CRP levels of 0–4.9 mg/dL, 7 of 10 (70%) in the group with CRP levels of 5.0–9.9 mg/dL, and 4 of 8 (50%) in the group with CRP levels of 10 mg/dL or higher. The higher the CRP levels, the lower the spontaneous passage rates ($p < 0.001$). Concerning neutrophil percentages, the number of patients whose ureteral stones were naturally passed was 121 of 128 (94.5%) in the normal group and 49 of 59 (83.1%) in the higher neutrophil percentage group. Spontaneous passage rates were lower in the higher neutrophil percentage group than in the normal neutrophil percentage group ($p = 0.011$) (Table 2).

In the multivariate analysis, we examined the relation

TABLE 1. Comparison of patient characteristics according to success of spontaneous passage

Characteristic	Spontaneous passage (+)	Spontaneous passage (-)	p-value
No. of patients	170	17	
Age (y)	46.6±12.2	50.2±14.6	0.267 ^a
Male/female	108/62	10/7	0.943 ^b
Left/right	87/83	8/9	0.901 ^b
Stone size (mm)	3.7±1.2	4.4±2.2	0.116 ^a
Location			
Upper ureter	20	6	
Mid ureter	83	7	0.023 ^c
Lower ureter	67	4	
C-reactive protein (mg/dL)	4.1±2.5	8.3±2.3	0.214 ^a
Neutrophil proportion (%)	55±12	46±15	0.343 ^a

Values are presented as mean standard±deviation or number. ^a:Student t-test. ^b:Chi-square test. ^c:Linear by linear association.

TABLE 2. Comparison of results according to serum C-reactive protein (CRP) level and neutrophil percentage

Variable	Spontaneous passage (+)	Spontaneous passage (-)	p-value
CRP (mg/dL) ^a			0.025
0-4.9	159 (94.1)	10 (5.9)	
5.0-9.9	7 (70.0)	3 (30.0)	
≥ 10	4 (50.0)	4 (50.0)	
Total	170 (100)	17 (100)	
Neutrophil (%) ^b			<0.001
Normal	121 (94.5)	7 (5.5)	
High (>74%)	49 (83.1)	10 (16.9)	
Total	170 (100)	17 (100)	

Values are presented as number (%). Fisher exact test.

Normal range: ^a:CRP, 0-0.5 (mg/dL); ^b:Neutrophil, 38-74%.

between each risk factor and the spontaneous passage of ureter stones. The passage rate was lower ($p < 0.001$) when CRP was higher and when the neutrophil percentage was higher (Table 3).

DISCUSSION

Ureteral stones are very common, and 10% to 15% percent of the population is diagnosed once or more in their lifetime [3,4]. Diverse treatment methods are used according to the size, location, and clinical aspects of the stone. These treatments include conservative management, which is applied with an expectation of natural stone passage; extracorporeal shock wave lithotripsy; ureteroscopy; and ureteral stone removal through laparotomy. Making the decision of whether to use conservative management or an aggressive treatment method is difficult. According to the American Urological Association, meta-analyses of different studies showed that 98% of stones less than 5 mm in size are passed spontaneously with conservative management [5]. It is best if a successful result can be obtained by using a non-invasive treatment method such as conservative management. However, if the conservative management fails, invasive treatment would have been better. Therefore, use of a factor that could help in the prediction of treatment success would be conducive to treatment selection.

Obstruction by a ureteral stone triggers ureteral edema, infection, and convulsion in the distal area of the stone and these factors interfere with the spontaneous passage of ureteral stones. Drug treatment to relieve such symptoms is a theoretical ground for conservative management. Other grounds for conservative management presented by Jang and Hong [6] are the inhibition of ureter contraction, increase in urinary flow rates, and decrease in ureteral edema. As a conservative management, drug treatment such as with nonsteroidal anti-inflammatory drugs and terpene compounds relieves inflammatory responses and ureteral convulsion or edema, thus preventing the congestion of the stone and relieving pain when the stone is

TABLE 3. Multivariate logistic regression analysis for estimating spontaneous passage of a ureteral stone

Variable	Adjusted odds ratio	95% Confidence interval	p-value
Size (mm), (≤ 4 , > 4)	0.449	0.136-1.486	0.190
Location (upper-mid, lower)	0.435	0.122-1.547	0.198
C-reactive protein (0-4.9, ≥ 5.0)	0.083	0.024-0.291	<0.001
Neutrophil (normal, higher)	0.297	0.098-0.903	0.032

discharged.

Many reports have dealt with treatment outcomes of predictive factors such as the size and location of a ureteral stone in order to judge the success of conservative management. Research has been conducted on the treatment outcomes of medications for spontaneous passage that relieve inflammatory responses from ureteral convulsion and edema resulting from obstruction caused by a ureteral stone [7-10], but no research has dealt with whether conservative management was successful in relation to serum CRP levels and neutrophil percentages.

The term *CRP* was first described by William Tillet in 1930 as a protein that precipitated streptococcus pneumoniae C-polysaccharide. Serum CRP is synthesized largely in the liver when stimulation such as an inflammatory response is given. When the stimulation disappears, serum CRP rapidly decreases. It has been used for a long time for clinical purposes to predict the degree of inflammation and infection [11]. Inflammatory responses in the proximal part of the ureter due to a ureteral stone may increase serum CRP levels, and indirect identification of the degree of inflammation may be used to predict the spontaneous passage rate and thus may be helpful in treatment selection. In a prospective study of ureteral stone patients with colicky pain, Angulo et al. [12] noted that in consideration of sensitivity and specificity, serum CRP levels of 2.8 mg/dL were the standard for initiating aggressive treatment. In the present study as well, when CRP levels were less than 0-4.9 mg/dL, ureteral stone removal rates were high, which suggests that conservative management may be preferred when CRP levels are low.

Neutrophils are a kind of white blood cell that include granulocytes with neutrally staining granules and tend to increase by acute bacterial infections, inflammatory responses, cardiovascular diseases such as myocardial infarction, and burns. In the case of obstruction by a ureteral stone, inflammatory responses increase neutrophil percentages. Sfoungaristos et al. [13] reported that leukocytosis might decrease spontaneous stone passage ($p=0.013$). In the present study as well, when neutrophil percentages were high, spontaneous passage rates were significantly low. In ureteral stone diagnosis, measuring the neutrophil percentage will be helpful for predicting the success rates

of natural stone passage.

In the diagnosis of ureteral stones, it may become possible to predict whether natural stone passage may occur in consideration of serum CRP levels and neutrophil percentages, which increase in inflammatory responses. If it is possible, treatment by conservative management has the merits of saving medical costs relative to interventions or surgical treatments and of patients performed activities of daily living and receiving treatment concurrently. Research has been conducted on cost-efficient treatment approaches to ureteral stones in the West as well [14,15]. According to the present study results, aggressive treatment of those with high CRP levels and neutrophil percentages from the moment of their diagnosis will result in efficient treatment outcomes and selection can be readily made by the presentation of objective standards for treatment methods.

The present study had the limits of failing to deal with the relationship between the size and location of a ureteral stone and spontaneous passage rates. Additional research that complements the present study and that includes a larger number of patients is considered necessary. Also, research on whether removal rates vary according to aggressive treatments such as extracorporeal shock wave lithotripsy in addition to spontaneous passage is needed.

CONCLUSIONS

Prediction of success rates in the treatment of small ureteral stones greatly influences the selection of treatment options. Measuring serum CRP levels and neutrophil percentages is useful for predicting whether spontaneous ureteral stone passage will be successful. More aggressive treatment methods such as extracorporeal shock wave lithotripsy should be considered when serum CRP levels and neutrophil percentages are high.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

REFERENCES

1. Parmar MS. Kidney stones. *BMJ*. 2004;328:1420-4.
2. Holdgate A, Pollock T. Nonsteroidal anti-inflammatory drugs (NSAIDs) versus opioids for acute renal colic. *Cochrane Database Syst Rev* 2004;(1):CD004137.
3. Elton TJ, Roth CS, Berquist TH, Silverstein MD. A clinical prediction rule for the diagnosis of ureteral calculi in emergency departments. *J Gen Intern Med* 1993;8:57-62.
4. Stewart C. Nephrolithiasis. *Emerg Med Clin North Am* 1988;6: 617-30.
5. Segura JW, Preminger GM, Assimos DG, Dretler SP, Kahn RI, Lingeman JE, et al. Ureteral Stones Clinical Guidelines Panel summary report on the management of ureteral calculi. The American Urological Association. *J Urol* 1997;158:1915-21.
6. Jang WK, Hong YK. The efficacy of furosemide-based medical expulsive therapy with tamsulosin and deflazacort for symptomatic distal ureter stones. *Korean J Urol* 2008;49:1013-7.
7. Yoon WY, Jeong TY, Lee SI, Kim DJ. Effect of tamsulosin and dichlozid on the expected treatment of ureteral calculi. *Korean J Urol* 2009;50:1213-8.
8. Porpiglia F, Destefanis P, Fiori C, Fontana D. Effectiveness of nifedipine and deflazacort in the management of distal ureter stones. *Urology* 2000;56:579-82.
9. Kim JW, Cho DY, Lee JG. Effect of tamsulosin on the expected treatment of upper and lower ureteral stones. *Korean J Urol* 2007;48:724-30.
10. Yilmaz E, Batislam E, Basar MM, Tuglu D, Ferhat M, Basar H. The comparison and efficacy of 3 different alpha1-adrenergic blockers for distal ureteral stones. *J Urol* 2005;173:2010-2.
11. Pepys MB, Baltz ML. Acute phase proteins with special reference to C-reactive protein and related proteins (pentaxins) and serum amyloid A protein. *Adv Immunol*. 1983;34:141-212.
12. Angulo JC, Gaspar MJ, Rodriguez N, Garcia-Tello A, Torres G, Nunez C. The value of C-reactive protein determination in patients with renal colic to decide urgent urinary diversion. *Urology* 2010;76:301-6.
13. Sfoungaristos S, Kavouras A, Katafigiotis I, Perimenis P. Role of white blood cell and neutrophil counts in predicting spontaneous stone passage in patients with renal colic. *BJU Int* 2012;110(8 Pt B):E339-45.
14. Lotan Y, Cadeddu JA, Roerhborn CG, Pak CY, Pearle MS. Cost-effectiveness of medical management strategies for nephrolithiasis. *J Urol* 2004;172(6 Pt 1):2275-81.
15. Lotan Y, Cadeddu JA, Pearle MS. International comparison of cost effectiveness of medical management strategies for nephrolithiasis. *Urol Res* 2005;33:223-30.