Original Article

Relationship between the spontaneous passage rates of ureteral stones less than 10 mm and serum C-reactive protein levels, white blood cell count and neutrophil percentages

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Keywords:
C-Reactive protein, White blood cell count, Neutrophil, medical expulsive therapy

Abstract

Objective: To determine the association between the spontaneous passage rates of ureteral stones less than 10 mm and serum C-reactive protein levels, white blood cell count and neutrophil percentages.

Material and Method: A prospective study was performed in 139 patients who were diagnosed with ureteral stones less than 10 mm in size from March 2016 – January 2017 at Phramongkutklao Hospital. Serum C-reactive protein, white blood cell count and neutrophil percentages were investigated before starting medical expulsive therapy. All patients were followed up at 4 weeks for spontaneous stone passage. The relationship between these factors and spontaneous stone passage were then examined.

Result: The spontaneous ureteral stone passage rates of the normal serum C-reactive protein level group (0-5 mg/dL) and the high serum c-reactive protein level group were 67% (59/88) and 47.1% (24/51), respectively (p=0.021). The passage rates of ureteral stones in the normal white blood cell count group and the high white blood cell count group were 54.6% (65/109) and 60% (18/30), respectively (p=0.971). The passage rates of ureteral stones in the group with a normal neutrophil percentage and in the group with a higher neutrophil percentage were 58.6% (65/111) and 64.3% (18/28), respectively (p=0.581). On multivariate analysis, normal serum C-reactive protein level (OR=3.27, p=0.008), decreased age (OR=0.97, p=0.019), smaller stone size (OR=0.61, p<0.001) and distal ureteral stones (OR=2.36, p=0.048) were associated with spontaneous ureteral stone passage.

Conclusion: Serum C-reactive protein level has a potential role to play in predicting spontaneous stone passage in patients with ureteral stones less than 10 mm.

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นิพนธ์ต้นฉบับ

ความสัมพันธ์ระหว่างอัตราการหลุดเองของนิ่วในท่อไตขนาดน้อยกว่า 10 มิลลิเมตรและระดับค่า C-Reactive protein, จำนวนเม็ดเลือดขาวและร้อยละของเม็ดเลือดขาวชนิดนิวโตรฟิลในเลือด

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คำสำคัญ:
C-Reactive protein, เม็ดเลือดขาว, เม็ดเลือดขาวชนิดนิวโตรฟิล, ยาช่วยการหลุดเองของนิ่วในท่อไต

บทคัดย่อ

วัตถุประสงค์: เพื่อศึกษาความสัมพันธ์ของระดับค่า C-Reactive protein จำนวนเม็ดเลือดขาวและร้อยละของเม็ดเลือดขาวชนิดนิวโตรฟิลในเลือดกับการหลุดเองของนิ่วในท่อไตที่มีขนาดน้อยกว่า 10 มิลลิเมตร

ผู้ป่วยและวิธีการศึกษา: เป็นการศึกษาแบบไปข้างหน้าในผู้ป่วยที่ถูกวินิจฉัยว่าเป็นนิ่วในท่อไตขนาดน้อยกว่า 10 มิลลิเมตร จำนวนทั้งหมด 139 ราย ที่ได้รับการรักษาในโรงพยาบาลพระมงกุฎเกล้า ในระหว่างมีนาคม 2559-มกราคม 2560 โดยได้รับการตรวจหาระดับค่า C-Reactive protein จำนวนเม็ดเลือดขาวและร้อยละของเม็ดเลือดขาวชนิดนิวโตรฟิลในเลือด ก่อนที่จะได้รับการรักษาด้วยยาช่วยการหลุดเองของนิ่วในท่อไต โดยมีการติดตามผู้ป่วยไปอีก 4 สัปดาห์ เพื่อประเมินการหลุดเองหรือไม่หลุดเองของนิ่วในท่อไต จากนั้นจึงหาความสัมพันธ์ระหว่างปัจจัยดังกล่าวและการหลุดเองของนิ่วในท่อไต

ผลการศึกษา: ในผู้ป่วยที่มีระดับค่า C-Reactive protein ปกติ (0-5 mg/dL) และสูงกว่าปกติ พบการหลุดเองของนิ่วในท่อไตร้อยละ 67 (59/88 ราย) และร้อยละ 47.1 (24/51 ราย) ตามลำดับ (p=0.021) ผู้ป่วยที่มีจำนวนเม็ดเลือดขาวระดับปกติ และสูงกว่าปกติในเลือด พบการหลุดเองของนิ่วในท่อไต ร้อยละ 54.6 (65/109 ราย) และร้อยละ 60 (18/30 ราย) ตามลำดับ (p=0.971) สำหรับผู้ป่วยที่มีร้อยละของเม็ดเลือดขาวชนิดนิวโตรฟิลระดับปกติ และสูงกว่าปกติในเลือด พบการหลุดเองของนิ่วในท่อไต ร้อยละ 58.6 (65/111 ราย) และร้อยละ 64.3 (18/28 ราย) ตามลำดับ (p=0.581) จากการวิเคราะห์หลายตัวแปร พบว่า ระดับค่า C-Reactive protein ที่ปกติ (OR=3.27, p=0.008) อายุของผู้ป่วยที่น้อยลง (OR=0.97, p=0.019) ขนาดของนิ่วในท่อไตที่เล็กลง (OR=0.61, p<0.001) และนิ่วในท่อไตส่วนปลาย (OR=2.36, p=0.048) สัมพันธ์กับการหลุดเองของนิ่วในท่อไต

สรุป: ระดับค่า C-Reactive protein ในเลือดของผู้ป่วยที่เป็นนิ่วในท่อไตขนาดน้อยกว่า 10 มิลลิเมตร ช่วยในการทำนายการหลุดเองของนิ่วในท่อไตได้ โดยระดับค่า C-Reactive protein ที่สูงกว่าปกติ จะมีผลทำให้โอกาสการหลุดเองของนิ่วในท่อไตน้อยลง

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Introduction

A urinary stone disease is a relatively common condition from which 2 to 20% of the worldwide population suffer and ureteral stones have a prevalence rate of 3 to 5%[1,2]. The presence of a ureteral stone is associated with abdominal pain or back pain, hematuria (blood in urine), nausea, vomiting and urinary tract infection (UTI)[3,4]. At present, the main treatment options are conservative treatment by medical expulsive therapy (MET), extracorporeal shockwave lithotripsy (ESWL), ureteroscopy and open surgery[5].

In the selection of a therapeutic method, the characteristic of the stone, severity of patient symptoms, anatomy of the collecting system, availability of instruments and patient preference should be considered. In particular, the spontaneous passage rate of a ureteral stone is high in a patient with a small ureteral stone. It is possible that the selection of an invasive approach at an early stage might constitute overtreatment and expose the patient to complications after the intervention[6]. Therefore, identifying predictive factors would aid the urologist in deciding whether to manage the patient conservatively or not.

Serum C-reactive protein (CRP) levels, white blood cell count (WBC) and neutrophil percentages are important factors that indicate inflammatory responses in the human body and are clinically used as an index of the degree of inflammation[4]. Ureteral stones can cause ureteral obstructions and trigger inflammatory changes in the proximal submucosal layer and thus prevent the passing of the stone[7]. In the current prospective study, we aimed to examine the increases in serum CRP levels, WBC and neutrophil percentages in relation to the success rates of spontaneous passage during conservative treatment. In order to look at the effects of the degree of inflammation in the ureter on the treatment of a ureteral stone less than 10 mm, we analyzed the relationship between spontaneous passage rates of ureteral stones, serum CRP levels, WBC and neutrophil percentages.

Materials and methods

The study was approved by the institutional ethics committee. A prospective study was performed in 139 patients who were diagnosed with ureteral stones less than 10 mm in size at the urology outpatient department, Phramongkutklao Hospital from March 2016 - January 2017. We analyzed laboratory and imaging parameters that may predict spontaneous stone passage over a period of 4 weeks after medical expulsive therapy (MET). Serum CRP, WBC and neutrophil percentages were investigated before starting MET. The study design had 2 objectives: Firstly, to evaluate the relationship between spontaneous stone passage and these laboratory parameters, and secondly to analyze the relationship between stone factors (size and location) and spontaneous stone passage.

Patient age and gender were recorded. Blood samples were obtained before starting treatment by MET and data regarding serum CRP, WBC and neutrophil percentages were recorded. Normal values of the above laboratory data, as presented by the Microbiology Department of Phramongkutklao Hospital, are the following: serum CRP 0-5 mg/dL, WBC 3,500-10,500 cells/mm^3 and neutrophil percentages 38-74%.

A plain abdominal film of kidney, ureter and bladder (KUB) was made for the diagnosis of ureteral calculi in all patients. When a radiopaque stone was identified, the size (in mm), the side (right or left) and the location were recorded. Location was assessed by ureter topography which was defined as upper ureter (above sacroiliac joint) and lower ureter (below sacroiliac joint). In those cases in which plain KUB was unable to identify a ureteral stone and when diagnosis was doubtful, intravenous pyelography (IVP) or a non-contrast computed tomography (CT) scan was performed. When a stone was found, size, side and location were recorded.

Exclusion criteria were patients with fever (axillary temperature more than 38°C) at the time of

examination, a history of recently diagnosed infection, antibiotic therapy or non-steroidal anti-inflammatory drug (NSAIDs) intake in the last 2 weeks, or an operation in the last 2 months. Patients who could not take MET (doxazosin) due to its side effects or poor compliance were excluded from the study. When the insertion of a ureteral stent or a percutaneous nephrostomy was necessary, these patients were excluded. Patients with organic diseases that could affect the values of the data collected (congenital urinary anomalies, chronic renal failure, chronic inflammatory diseases, etc), patients with renal colic but with no stone to be found in imaging techniques, and those with more than one stone found were not recorded. All patients had a solitary ureteral stone.

A standard MET protocol was followed in all patients consisting of 1 tablet of doxazosin 2 mg orally at night, and NSAIDs, such as ibuprofen 400 mg or diclofenac, orally after meals as a conservative management for pain relief. Spontaneous stone passage was defined as no stone seen on an imaging test within 4 weeks after the diagnosis of a ureteral stone and the start of conservative management.

Patient characteristics were investigated using the Student t-test, chi-square test, and linear by linear test. A univariate analysis was performed to identify the significance of age, gender, stone side, location and size, serum CRP, serum total WBC count and neutrophil percentages. The association between the above factors and spontaneous stone passage rates was investigated. Multivariate logistic regression analysis was conducted using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, USA). A p-value < 0.05 was considered statistically significant.

Results

Patient characteristics are shown in Table 1. Of the 139 patients included for analysis, spontaneous stone passage was observed in 83 (59.7%) patients. There were no significant differences in gender, stone side, total WBC count and neutrophil percentages. The significant differences were age, stone location, stone size and serum CRP levels (Table 1). In relation to serum CRP levels, the number of patients whose ureteral stones were spontaneously passed was 59 of 88 (67%) in the group with normal serum CRP levels (0-5 mg/dL) and 24 of 51 (47.1%) in the group with high serum CRP levels (p=0.021). In the univariate analysis (Table 2), spontaneous stone passage was significantly associated with male patients (p=0.031), younger age (p=0.003), stones located in the lower ureter (p=0.002) and smaller stones (p<0.001).

In the multivariate analysis, age (year) [odds ratio(OR) 0.97; 95% confidence interval (CI): 0.94-0.97; p=0.019], size of stone (OR 0.61; 95% CI: 0.47-0.78; p<0.001), stone location (lower vs. upper ureter) (OR 2.36; 95% CI: 1.01-5.53; p=0.048) and serum CRP levels (0-5 mg/dL vs. >5 mg/dL) (OR 3.27; 95% CI: 1.37-7.8; p=0.008) were found to be independent predictors of spontaneous ureteral stone passage (Table 3).

Discussion

Various treatment methods are available for ureteral stones, varying from conservative treatment by watchful waiting and MET or minimally invasive management, such as ESWL and ureteroscopy, to more invasive interventions (open or laparoscopic surgery). The advances of minimally invasive techniques have resulted in their wide adoption for the treatment of ureteral stones and their efficacy has been proven by several studies[8-10]. Both ESWL and ureteroscopy have high success rates, reaching 63-86% and 57-92% of stone clearance, respectively[9,10]. However, these treatment methods are not complication free and add significantly to the cost of treatment[8,9,11,12]. Avoiding complications from interventions, or merely compliance with medication, are of concern to both the physician and patient. However, the problem is how and when to make the decision. Delaying the decision can be associated with an increased risk of complications such as recurrent attacks of renal colic, urinary tract

infections, and renal function deterioration. Therefore, use of a factor that could help in the prediction of treatment success would be conducive to treatment selection.

Many studies have dealt with the treatment outcomes of predictive factors, such as the size and location of a ureteral stone, in order to evaluate the success of conservative management[13-16]. In a prospective study of ureteral stone patients with renal colic, Angulo et al.[17] notes that in consideration of sensitivity and specificity, serum CRP levels of 2.8 mg/dL were the standard for initiating aggressive treatment. Similarly, Park et al.[7] found that high serum CRP levels (more than 5 mg/dL) were a predictor of a low rate of spontaneous ureteral stone passage. In our study, the spontaneous ureteral stone passage rates were low in patients with high serum CRP levels (>5 mg/dL). Our results are consistent with previous results. A possible explanation of the above findings may be that increases in their levels depict the degree of inflammation caused to the ureteral mucosa during the passage of a stone, since it has been observed that the interaction between the mucosa of the ureter and the stone induces inflammation at the stone site[18].

From a retrospective study of 187 patients, Park et al.[7] found that when neutrophil percentages were high (>74%), spontaneous passage rates were significantly low. They hypothesized that a ureteral stone causes swelling of ureteral mucosa and finally obstruction. These interactions could increase inflammatory responses and increase neutrophil percentages. However, the present results did not give the same conclusions and the neutrophil percentages did not seem to be a significant factor for spontaneous stone passage.

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

Patients' characteristics	Stone passing (+)	Stone passing (-)	p-value
No. of patients	83	56	-
Age (year)	44.53 ± 15.62	52.62 ± 15.24	0.003
Gender			0.031
M	58 (66.7%)	29 (33.3%)	
F	25 (48.1%)	27 (51.9%)	
Side of stone			0.212
Right	37 (54.4%)	31 (45.6%)	
Left	46 (64.8%)	25 (35.2%)	
Location			0.002
Upper ureter	23 (43.4%)	30 (56.6%)	
Lower ureter	60 (69.8%)	26 (30.2%)	
Stone size (mm)			
Mean ± SD (IQR)	4.23 ± 1.49	5.84 ± 1.92	< 0.001
C-reactive protein (mg/dL)	2.4 (1.1, 5.5)	4.75 (1.85, 14.5)	0.002
WBC (cell/mm^3)	8400 (6700, 9800)	7900 (6750, 9600)	0.344
Neutrophil percentages (%)	63.55 ± 11.92	62.6 ± 11.21	0.584

Table 2. Comparison of the results according to serum CRP levels, WBC count and neutrophil percentages

Variable	Stone passing (+)	Stone passing (-)	p-value
CPR (mg/dL)			0.021
0-5	56 (67%)	29 (33%)	
>5	24 (47.1%)	27 (52.9%)	
WBC (cell/mm^3)			0.971
Normal (3,500-10,500)	65 (54.6%)	44 (45.4%)	
Abnormal	18 (60%)	12 (40%)	
Neutrophil percentages (%)	63.55 ± 11.92	62.6 ± 11.21	0.581
Normal (38-74)	65 (58.6%)	46 (41.4%)	
Abnormal	18 (64.3%)	10 (35.7%)	

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

Variable	Adjusted odds radio	95% Confidence interval	p-value
Gender (Male)	1.51	0.62 - 3.66	0.368
Age (year)	0.97	0.94 - 0.99	0.019
Location (Lower ureter)	2.36	1.01 - 5.53	0.048
Stone size (mm)	0.61	0.47 - 0.78	<0.001
Serum (mg/dL)	3.27	1.37 - 7.8	0.008

In a prospective study of 265 patients, Sfoungaristos et al.[5] found that WBC count was a highly significant contributing factor for predicting spontaneous stone passage. However, the present study results do not seem to be a significant predictor of spontaneous ureteral stone passage.

Apart from the serum CRP levels, WBC count and neutrophil percentages, there are several other factors that are significant predictors of spontaneous stone passage. In our study we found that younger age, smaller stone size and lower ureteral stones statistically significantly predicted spontaneous stone passage. These results confirmed the previous findings[19-21].

From the present study results, aggressive treatment of those with high serum CRP levels 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 has some limitations. We did not perform a non-contrast CT in most patients if plain KUB or IVP revealed the stone. 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 levels. Finally, the level of compliance was difficult to confirm in all patients with respect to fluid intake; patients were asked to consume at least 2 L of fluids daily.

In conclusion, the serum CRP levels, stone size and location were independent predictors of spontaneous stone passage in patients with ureteral stones less than 10 mm in size. Early urologic intervention, rather than MET, may be considered for patients presenting with high serum CRP levels at an initial stone episode.

Conflict of interest

This study has no conflict of interest.

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