

Stone Expulsion Rate of Small Distal Ureteric Calculus Could Be Predicted With Serum C-Reactive Protein, White Cell Counts And Neutrophil Percentage: A Prospective Study

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Abstract

Purpose: To determine the relationship between stone expulsion rate of distal ureteric calculus less than or equal to 10mm in size and C reactive protein (CRP) level, white cell count and neutrophil percentage.

Materials and Methods: A total of 143 patients with distal ureteric calculus of ≤ 10 mm were evaluated for stone expulsion rate and its correlation with serum CRP, white cell count and neutrophil percentage. All patients received tablet Tamsulosin 0.4mg for 4 weeks or till the expulsion of stone. Patients were called weekly till 4 weeks, or early if there was history of stone expulsion. Patients were divided in two groups according to normal and elevated CRP levels, white cell count and neutrophil percentage at baseline for statistical analysis.

Results: The patients had an average age of 35.6 ± 13.9 years. 52.4% were male. Ratio of right to left was 1.38:1. Majority of the patients with distal ureteric calculus ≤ 10 mm passed their stone (78.3 %) with medical expulsion therapy. Expulsion of stone less than 5mm was statistically significant ($p 0.013$). Patients with normal neutrophil percentage and normal CRP level had higher stone expulsion rate than elevated neutrophil or CRP (96.6% vs. 48.1, 93.9% vs. 44.4% respectively). In patients with normal white cell count, 89.7% passed their stone while in elevated white cell count group 44.4% passed their stone.

Conclusion: In our study, patients with distal ureteric calculus of ≤ 10 mm with normal CRP level and normal neutrophil count had higher expulsion rate while WBC count showed no statistically significant association.

Keywords: C-reactive protein, distal ureteric stone, neutrophil percentage, stone expulsion

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I. Introduction

Urolithiasis affects 8–15% of the world population (Dellabella et al, 2003), of which ureteric stones account for 20%, and almost 70% of these are distal ureteric stones (Erturhan et al, 2007). Diverse treatment methods for ureteric stones exist like watchful waiting with or without addition of medical expulsive therapy (MET), extracorporeal shockwave lithotripsy (ESWL) and Ureterscopy with Intra-Corporeal Lithotripsy. The fact that most ureteric stones can pass spontaneously, application of minimally invasive techniques can be considered overtreatment adding unnecessary costs and complications (Segura et al, 1997). MET though is a simple and cost effective treatment, it has complications like acute renal failure, febrile infections and recurrent ureteric colic (Gandhi and Agrawal, 2013). If predictive factors could be identified for whether the spontaneous passage of a ureteral stone can be expected, it would be helpful for meticulous selection of treatment method. The two most widely studied factors for spontaneous stone passage are stone size and its location. When ureteric stone pass through its course, it causes local inflammation, leading to increase in acute phase proteins like serum C-reactive protein (CRP), white cell count and neutrophil percentage, which may be used to predict the spontaneous passage rate. Studies has been done for potential predictors of ureteric stone expulsion favoring C-reactive protein but conflicting results for white cell count and neutrophil percentage (Angulo et al, 2009; Hussein, 2011 and Sfoungaristos et al, 2012). Hence, this study was conducted to know the relationship between stone expulsion rate of distal ureteric stone with C-reactive protein, white cell count and neutrophil percentage.

II. Materials And Methods

This prospective study was conducted at the B.P. Koirala Institute of Health Sciences, Dharan, Nepal, between June 2015 and June 2016 with approval by 'The Institute Protocol and Ethical Committee'. All patients above 18 years with distal ureteric stone less than or equal to 10mm were included. Patients with acute or chronic febrile infection, moderate to severe hydronephrosis, chronic renal insufficiency, pyonephrosis,

Solitary kidney with stone, anatomical malformation of renal system, neoplasia, liver failure, multiple ureteric stone, diabetes mellitus, hypertension, pregnancy, hypersensitivity to Tamsulosin, Proximal or middle ureteric calculi and those who did not give consent were excluded.

As previously reported by **Park et al, (2013)**, spontaneous ureteric stone expulsion in patients with normal CRP was 90.9% whereas 58.8% had no spontaneous expulsion among high CRP group. The sample size was calculated with RR 1.5, power 80%, α -error 5%; using 2-sided test, minimally 34 patients were required in each group. However, we included a total of 143 patients as the study considered multiple variables.

A prior written informed and well understood consent was taken from all eligible patients after explaining about the conservative treatment, possible adverse effects of the drug and possible outcomes. Ureteroscopy and intracorporeal lithotripsy was also suggested as alternative therapeutic option.

Investigations like complete and differential blood counts, C-reactive protein level, urine routine and microscopic test and urine culture sensitivity was done. Radiological examinations like X-ray Kidney-Ureter-Bladder (KUB), Ultrasonography (USG) of the urinary tract was done in all patients. CT Urography and Non-contrast enhanced computed tomography (NCCT) was done as and when indicated. The result of investigations was noted in the preset Proforma. Normal and elevated CRP was defined as $<6\text{mg/dL}$ and $>6\text{mg/dL}$ respectively. Normal and elevated white cell count was defined as 4000-11000 cells/cc and >11000 cells/cc respectively. Normal and elevated neutrophil percentage was defined as 50-75% and $>75\%$ respectively. Patients were divided in two groups according to normal and elevated CRP levels, white cell count and neutrophil percentage at baseline for statistical analysis. Size of the stone was measured by USG or KUB or CT, as maximum transverse diameter in millimeters and was noted. Location of distal ureteric stone was defined from the lower border of the sacrum to the bladder. C-reactive protein level, white cell count and neutrophil percentage was estimated before administration of the anti-inflammatory drug. All patients were given tablet Tamsulosin for 4 weeks or till the expulsion of stone. Tablet Ketorolac was given thrice daily, till the pain subsided. In cases where the pain didn't subside with oral drug he/she was switched to injectable Ketorolac. In addition all patients were asked to drink at least 2 liters of water daily. Patients were advised to filter the urine to observe possible stone expulsion.

Patients were called weekly till 4 weeks, or early if there was history of stone expulsion. Detailed history about expulsion of stone was taken, and he/she underwent x-ray KUB and USG, CT urography for presence or absence of stone, and results were noted. Stone expulsion was defined as no stone seen on x-ray KUB, USG and CT. Duration for the expulsion of stone was also noted in the preset Proforma. The adverse effects of the drugs, if any, was recorded during follow up.

III. Statistical Analysis

Statistical analysis was performed by using mean, standard deviation, number, percentage for descriptive analysis. Bivariate analysis was done by using student t-test and chi-square test for continuous variable and categorical variables respectively to compare between 2 groups of spontaneous expulsion of stone. Multivariate analysis was done using multiple logistic regressions. A value of $p < 0.05$ was considered significant.

IV. Results

In BPKIHS urosurgery outpatient department, a total of 290 patients presented with ureteric stones of which 143 patients fulfilled the inclusion criteria and were included in the study.

The mean age of the patients in our study was 35.6 ± 13.9 years (mean \pm SD). Most of the patients were in the age group of 20-39 years (55.9%). There was male predominance with male to female ratio of 1.10:1. Mean stone size was 6.6mm. Mean duration of symptoms was 15.8 days. Eighty three patients (58%) had stone on right side while sixty (42%) had stone on left side. Ratio of right to left was 1.38:1. Out of 143 patients, 112 (78.3%) passed their stone with medical expulsion therapy while 31 (21.7%) did not have stone expulsion and underwent Ureterorenoscopy and intracorporeal lithotripsy.

Table 1: Spontaneous expulsion of the stone with medical expulsive therapy

Size of stone	Spontaneous expulsion + (%)	Spontaneous expulsion - (%)	X2 value	P-value
<5	36(92.3)	3(7.7)	6.178	0.013
5-10 mm	76(73.07)	28(26.92)		

Table 2: Spontaneous expulsion of the stone with medical expulsion therapy according to size

Stone passed	Stone size (mm)				
	1-5	5.1-6	6.1-7	7.1-9	9.1-10
Yes	36 (92.3%)	20 (74.1%)	17 (73.9%)	19 (73.1%)	20 (71.4%)
No	3 (7.7%)	7 (25.9%)	6 (26.1%)	7 (26.9%)	8 (28.6%)
Total	39	27	23	26	28

Table 3: Relationship of spontaneous expulsion of stone with white cell count

WBC (cells/cc)	Spontaneous expulsion (+) (%)	Spontaneous expulsion (-) (%)	X2 value	P-value
Normal (4000-11000)	96(89.7)	11 (10.3)	32.521	0.001
High (>11000)	16(44.4)	20 (55.6)		

Table 4: Relationship of spontaneous expulsion of stone with neutrophil percentage

Neutrophil percentage (%)	Spontaneous expulsion (+) (%)	Spontaneous expulsion (-) (%)	X2 value	P-value
Normal (50-75)	86 (96.6)	3 (3.4)	46.525	0.001
High (>75)	26 (48.1)	28(51.9)		

Table 5: Relationship of spontaneous expulsion of the stone with CRP level

CRP (mg/L)	Spontaneous expulsion (+) (%)	Spontaneous expulsion (-) (%)	X2 value	P-value
Normal (≤6)	92 (93.9)	6 (6.1)	44.384	0.001
High (>6)	20(44.4)	25 (55.6)		

Table 6: Relationship of spontaneous expulsion of stone with medical expulsive therapy and urine culture

Urine culture	Spontaneous expulsion(+) (%)	Spontaneous expulsion(-) (%)	X2 value	P-value
Sterile	106 (79.1)	28 (20.9)	0.768	0.381
Growth	6 (66.7)	3 (33.3)		

The number of patients with spontaneous expulsion of stone was 112 (78.3%). There were no significant differences between age and gender (p-value 0.761 and 0.359 respectively). Significant differences were present in stone side (p-value 0.039), CRP level (p-value 0.001), neutrophil percentage (p-value 0.001) and white cell count(p-value 0.001).

Table 7: Comparison of patient characteristics according to success of spontaneous expulsion of stone

Characteristics	Spontaneous expulsion (+)	Spontaneous expulsion (-)	p-value
Number of patients (n)	112	31	
Age (y)	35.49±13.75	36.35±14.81	0.761
Male/Female	61/51	14/17	0.359
Left/Right	52/60	8/23	0.039
CRP (mg/L)			
Normal (≤6)	92	6	0.001
High (>6)	20	25	
White cell count (cells/cc)			
Normal (4000-11000)	96	11	0.001
High (>11000)	16	20	
Neutrophil percentage (%)			
Normal(50-75)	86	3	0.001
High(>75)	26	28	

Patients with distal ureteric stone ≤10mm on right side, normal CRP level, normal white cell count and normal neutrophil percentage had high chances of spontaneous expulsion with medical expulsion therapy (Table7). The variable which were significantly associated with spontaneous expulsion of distal ureteric stone with p-value less than 0.20 from bivariate analysis were included into binary logistic regression, as shown in Table 8.

Table 8: Multivariate logistic regression analysis for estimating spontaneous passage of a ureteric stone

Variables	Adj. Odds Ratio	95% CI for OR		P value
		Lower	Upper	
Side (left/right)	0.351	0.110	1.121	0.077
CRP (normal/high)	0.169	0.051	0.561	0.004
WBC (normal/high)	0.343	0.102	1.154	0.084
Neutrophil percentage (normal/high)	0.131	0.027	0.628	0.011

V. Discussion

Ureteric stones are very common, and 10% to 15% percent of the population is diagnosed once or more in their lifetime (**Parket al, 2013**). 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 ureteric stone removal through laparotomy. The advances of minimal invasive techniques and their high success rate have resulted in its wide adoption for treatment of ureteric stone (**Grasso et al, 1998**). However they are costly and have complications. Conservative management is cheap but not complication free. Making the decision of whether to use either of treatment methods is difficult. Identification of factors that could help in the prediction of treatment success would be conducive to treatment selection therefore this prospective study was conducted to determine the relationship between the stone expulsion rates of distal ureteric stones less than or equal to 10mm with CRP level, white cell count and neutrophil percentage. One hundred and forty three patients were included. One hundred and twelve patients (78.3%) passed their stone with medical expulsion therapy. In patients with stone size less than 5mm, thirty six (92.3%) passed their stone while in patients with stone size of 5-10mm, seventy six (73.07%) passed their stone, $p < 0.013$ (table 1). Similar results were noticed by **Tchey et al, (2011)** where they reported stone expulsion rate as 71% for lower ureteric stones. Stones smaller than 6mm had 88.7% chance of spontaneous passage while stone 6mm or larger had 57.5% expulsion chances. In meta-analysis of different studies done by **Segura et al, (1997)**, mentioned that 98% of stone less than 5mm are passed spontaneously with conservative management. **Hussein, (2011)** reported incidence of spontaneous expulsion of distal ureteric stones as high as 71-98% for stone ≤ 5 mm and only 25-51% for stone more than 5mm.

Ninety six patients (89.7%) with normal white cell count passed their stone with medical expulsion therapy while 11 (10.3%) did not pass. Sixteen patients (44.4%) with high white cell count passed stone but 20 (55.6%) did not pass the stone, (Table 3). In bivariate analysis (Table 7), higher spontaneous expulsion of stone with normal white cell count was statistically significant (p value 0.001). However, after logistic regression (Table 8) white cell count was not significantly associated with stone expulsion (CI 0.102-1.154, p value 0.084). **Sfoungaristos et al, (2011)** reported a statistically significant higher expulsion rate with elevated white cell count. They gave a hypothesis that probably stones that are incapable of moving and passing forward in the ureter are producing minimal inflammation during renal colic, or at least a less significant reaction than that produced by a stone which is travelling down the ureter producing an inflammatory reaction along the ureter. Eighty six patients (96.6%) with normal neutrophil percentage passed their stone while 3 (3.4%) did not pass. Twenty six patients (48.1%) with high neutrophil percentage passed stone but 28(51.9%) did not pass their stone. Relationship of passage of stone with medical expulsion therapy and neutrophil percentage was statistically significant, p value 0.001 (Table 4) i.e. patients with distal ureteric calculus and high neutrophil percentage have less chance of spontaneous expulsion of their stone. Ureter obstruction caused by ureteric stone triggers inflammatory changes in the distal submucosal layer, leading to elevated neutrophil percentage and prevents spontaneous expulsion. **Park et al, (2013)** reported higher stone expulsion rate (94.5%) in normal neutrophil group. Spontaneous passage rates were lower in the higher neutrophil percentage group than in the normal neutrophil percentage group (p 0.011), which correlates with our study.

In contrast, **Sfoungaristos et al, (2012)** reported a statistically significant higher stone expulsion rate in patients with high neutrophil percentage. But they also emphasized that prolonged inflammation may decrease the ureteral compliance and luminal diameter hindering stone passage, as noted in our study.

In patients with normal CRP level, 92 (93.9%) patients passed their stone with medical expulsion therapy while 6 (6.1%) did not pass their stone. Twenty patients (44.4%) with high CRP level passed their stone while 25(55.6%) did not pass their stone, which was statistically significant, p value 0.001 (Table 5). **Angulo et al, (2010)** reported that patients of ureteric stone with low CRP level had higher expulsion rate when compared to high CRP level (p< 0.001)

Park et al, (2013) reported that the number of patients whose ureteric stones were naturally passed was 159(94.1%) out of 169 with serum CRP levels of 0-4.9 mg/dL, 7(70%) out of 10 with CRP levels of 5.0-9.9 mg/dL, and 4 (50%) out of 8 with CRP levels of 10 mg/dL or higher. The higher the CRP levels, the lower the spontaneous passage rates (p<0.001). Similarly **Hussein, (2013)** reported that patients with spontaneous stone expulsion had significantly lower serum CRP level than those who failed to pass the stone.

In patients with sterile urine, 106(79.1%) passed their stone with medical expulsion therapy but 28(20.9%) did not pass their stone. In patients with growth in urine 6 (66.7%) passed their stone while 3 patients (33.3%) did not pass their stone (Table 6). Patients of distal ureteric calculus with sterile urine have no relation of spontaneous expulsion of stone with medical expulsion therapy (p value 0.381).

In bivariate analysis we found that patients with distal ureteric stone ≤ 10 mm on right side, normal CRP level, normal white cell count and normal neutrophil percentage had high chances of spontaneous expulsion with medical expulsion therapy (Table 7). The variable which were significantly associated with spontaneous

expulsion of distal ureteric stone with p-value less than 0.20 from bivariate analysis were included into binary logistic regression.

On applying binary logistic regression in our study, it was observed that adjusted odds ratio for normal CRP and neutrophil percentage was 0.169 (0.051-0.561) and 0.131 (0.027-0.628) respectively. Thus, only two variables i.e. normal CRP level (p-value 0.004) and normal neutrophil percentage (p-value 0.011) were significantly associated with spontaneous expulsion of distal ureteric stone of ≤ 10 mm with medical expulsion therapy (Table 8). The meticulous selection of treatment modality for ureteric stone is important for better outcome. Patients during conservative management may experience recurrent renal colic, urine tract infection, sepsis and deterioration of renal function. On the other hand, many patients undergo unnecessary invasive intervention which are not complication-free and add significantly to the cost of treatment. Predictors of success rate are required for better selection of treatment modality. Present study revealed that CRP level and neutrophil percentage are important predictors for spontaneous expulsion of stone. Conservative management is preferred when CRP and neutrophil level is normal. However elevated values warrant aggressive management.

VI. Conflict Of Interest

The authors have nothing to disclose.

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