Evaluating Percutaneous Nephrolithotomy-Induced Kidney Damage by Measuring Urinary Concentrations of β-2 Microglobulin

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Purpose: To assess percutaneous nephrolithotomy (PCNL)-induced kidney tubular damage and the associated factors.

Materials and Methods: One hundred and eight patients who have undergone PCNL from May 2007 to October 2007 were recruited in this study. Urinary level of β2-microglobulin (Uβ2MG) was measured on the day before the operation as well as on the 1st and 7th post PCNL days. Percutaneous nephrolithotomy was performed using standard method. Patients' demographic and peri-operative data were collected to evaluate factors influencing renal injury.

Results: Median urinary levels of β2-microglobulin on pre-operative, 1st, and 7th postoperative days were 0.2 mg/dL (range, 0.1 to 82), 0.4 mg/dL (range, 0.2 to 97), and 0.2 mg/dL (range, 0.2 to 114), respectively. High levels of Uβ2MG (> 2.3 mg/dL) were observed in 10 (9%), 20 (19%), and 10 (9%) patients pre-operatively and on the 1st and 7th postoperative days, respectively. In multivariable analysis, Uβ2MG on the 1st postoperative day was associated with pre-operative serum creatinine level ($P < .001$) and diabetes mellitus ($P = .05$), while Uβ2MG on the 7th day after the operation was associated with pre-operative serum creatinine level ($P = .01$), diabetes mellitus ($P = .01$), and PCNL time ($P = .02$).

Conclusion: Percutaneous nephrolithotomy does not cause kidney tubular injury beyond one week. In patients with pre-operative high serum creatinine concentration, diabetes mellitus, and/or long operation time, the likelihood of the kidney damage is higher than others.

Keywords: percutaneous nephrolithotomy, beta 2-microglobulin, acute kidney injury

Urol J. 2011;8:277-82.
www.uj.unrc.ir

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Received March 2011
Accepted August 2011

INTRODUCTION

Different methods have been used to assess percutaneous nephrolithotomy (PCNL)-induced renal injury, including measurement of serum level of creatinine, creatinine clearance,[1,2] and nuclear scans, such as diethylenetriamine pentaacetic acid (DTPA), dimercaptosuccinic acid (DMSA), and mercaptuacetyltriglycine (MAG-3).[3-7] These markers demonstrate the changes in glomerular function of the kidneys after the PCNL, on which little work has been done, to the best of our knowledge.

Previous studies have shown that β-2 microglobulin is a more sensitive marker of renal tubular injury in comparison with serum creatinine level. Therefore, its measurement has been advocated

as an early marker of tubular injury.[8-12] Furthermore, unlike nuclear scans, concentrations of urinary β-2 microglobulin (Uβ2MG) are not influenced by urinary obstruction.[13] This study was aimed to assess PCNL-induced renal tubular injury by measuring Uβ2MG.

MATERIALS AND METHODS

This study was carried out on 108 patients with nephrolithiasis who underwent PCNL in Labbafinejad Medical Center in Tehran, Iran, from May 2007 to October 2007.

The reasons for PCNL were as follows: Obstructive kidney stones > 2 cm, failed extracorporeal shock wave lithotripsy (SWL), kidney stones with distal stenosis, and stones > 1 cm in proximal ureter and failed SWL. Percutaneous nephrolithotomy was done using standard method.

Urinary β-2 microglobulin was measured pre-operatively and on the 1st and 7th postoperative days by an immunoassaykit (MININEPHTM; The Binding Site Ltd., Birmingham, UK). The Uβ2MG samples on the 1st and 7th postoperative days were collected from the nephrostomy catheter and the voided urine sample, respectively. The normal reference range of Uβ2MG according to the manufacturer instructions is 0.3 to 2.3 mg/dL. Therefore, Uβ2MG values higher than 2.3 mg/dL were considered abnormal. Patients' demographic, laboratory, and peri-operative data were collected to identify factors correlated with Uβ2MG changes on postoperative days.

Statistical Analysis

The gathered data were analyzed using SPSS software (the Statistical Package for the Social Sciences, Version 16.0, SPSS Inc., Chicago, Illinois, USA). Two separate analyses were planned:

At first, changes in concentrations of Uβ2MG on the 1st and 7th postoperative days were compared with pre-operative values. The associations of Uβ2MG changes with independent categorical and qualitative variables were investigated by Mann-Whitney *U* test and Spearman correlation coefficient, respectively. The independent variables included age, gender, stone size, hypertension, ischemic heart disease and diabetes mellitus as well as pre-operative hydronephrosis, regional renal cortical atrophy, creatinine level, operation duration, and access numbers. Thereafter, significant variables were entered into two analysis of covariance models with dependent variables defined as Uβ2MG values on days 1 and 7 after the operation. Pre-operative Uβ2MG was used as a covariate to remove its effect.

The second analysis was restricted to patients with normal pre-operative serum creatinine level (group N). The associations of high postoperative Uβ2MG with independent variables were assessed by Chi-Square or Fisher's Exact tests, as appropriate. To obtain odds ratios for significant variables in group N, a logistic regression was used.

RESULTS

Patients' characteristics and peri-operative data are summarized in Table 1. Stone location was the renal pelvis in 27 (25.0%), lower calyx in 18 (16.6%), lower calyx and pelvis in 18 (16.6%), multiple calyces in 12 (11.1%), upper calyx in 3 (2.7%), staghorn in 22 (20.3%), middle calyx in 3 (2.7%), diverticulum in 2 (1.8%), and proximal ureter in 3 (2.7%) patients. Mild, moderate, and severe obstructive hydronephrosis due to the kidney stones were present on pre-operative intravenous pyelography in 18 (16.6%), 59 (54.6%), and 13 (12.0%) patients, respectively.

High Uβ2MG on the pre-operative day, 1st, and 7th postoperative days was found in 10 (9%), 20 (19%), and 10 (9%) patients, respectively. The 20 patients with high Uβ2MG on the 1st postoperative day included 10 patients with high and 10 with normal pre-operative Uβ2MG. All these patients had normal Uβ2MG on the 7th postoperative day, except one patient.

In bivariable analysis, Uβ2MG changes on the 1st day after the operation were associated with access numbers and operation time while on the 7th day, they were correlated with hydronephrosis severity, cortical atrophy, and pre-operative serum creatinine level (Table 2). In analysis of covariance, pre-operative serum creatinine level

Table 1. Patients' characteristics and peri-operative data

Characteristic	
Age (y), mean ± SD	44 ± 15
Gender (Male/Female), N/N	74/34
Stone size (mm), mean ± SD	2.6 ± 0.6
Pre-operative creatinine (mg/dL), median (range)	1.0 (0.1 to 3.6)
Pre-operative hemoglobin (g/dL), mean ± SD	14.0 ± 1.3
Pre-operative Uβ2MG (mg/dL), median (range)	0.2 (0.12 to 82)
History of stone intervention, N (%)	
SWL	37 (34)
PCNL	4 (4)
Open surgery	12 (11)
Multiple	12 (11)
Hypertension, N (%)	19 (18)
Diabetes, N (%)	5 (5)
Ischemic heart disease, N (%)	7 (7)
Access numbers, N (%)	
One	91 (84)
Two	17 (16)
Postoperative creatinine (mg/dL), median (range)	1.1 (0.5 to 4.1)
Hemoglobin drop (g/dL), median (range)	0.8 (0 to 6.1)
Operation duration (min), median (range)	40 (20 to 120)
Hospital stay (d), median (range)	4 (1 to 10)
Postoperative day 1 Uβ2MG (mg/dL), median (range)	0.4 (0.2 to 97)
Postoperative day 7 Uβ2MG (mg/dL), median (range)	0.2 (0.2 to 114)

SD indicates standard deviation; Uβ2MG, urinary β-2 microglobulin; SWL, extracorporeal shock wave lithotripsy; and PCNL, percutaneous nephrolithotomy.

and diabetes mellitus were statistically significant predictors of Uβ2MG on the 1st postoperative day ($P < .001$ and $P = .05$, respectively), while pre-operative serum creatinine level ($P = .01$), presence of diabetes mellitus ($P = .01$), and operation duration ($P = .02$) were significant predictors of the Uβ2MG on the 7th postoperative day (Table 2).

Group N included 98 patients with normal pre-operative serum creatinine level. All of these patients had normal pre-operative Uβ2MG. Ten (10%) patients in group N developed high Uβ2MG on the 1st day while only 1 patient had increased Uβ2MG levels on the 7th postoperative day. Therefore, we did not perform statistical analysis for factors contributing to increased Uβ2MG on the 7th postoperative day.

The factors contributing to high Uβ2MG on day 1 after the operation in this subgroup of patients with normal pre-operative Uβ2MG were analyzed (Table 3). Injury in this subgroup of patients was correlated with operation time and access numbers. On day 1, Uβ2MG levels significantly increased as operation time exceeded 40 minutes. Stone size was neither associated with pre-operative Uβ2MG nor operation

Table 2. Uβ2MG levels with respect to demographic and operative factors

Variables	Number	Pre-operative Uβ2MG, median (IQR) mg/dL	Postoperative Uβ2MG, median (IQR) mg/dL	
			day 1	day 7
Pre-operative Creatinine, mg/dL				
≤ 1.5	98	0.20 (0.20 to 0.23)	0.34 (0.20 to 1.07)†	0.20 (0.20 to 0.21)*†
> 1.5	10	13.5 (5.4 to 27.7)	12.5 (6.9 to 62.5)†	14.3 (6.7 to 58.5)*†
Pre-operative Hydronephrosis				
Moderate to Severe	72	0.20 (0.20 to 0.29)	0.50 (0.20 to 2.30)	0.20 (0.20 to 0.50)*
None to Mild	36	0.21 (0.20 to 0.29)	0.37 (0.20 to 1.09)	0.20 (0.20 to 0.20)*
Cortex Thickness				
Normal	53	0.20 (0.20 to 0.27)	0.23 (0.20 to 1.07)	0.20 (0.20 to 0.20)*
Decreased	55	0.20 (0.20 to 0.40)	0.53 (0.20 to 3.40)	0.20 (0.20 to 0.70)*
Operation Duration, min				
20 to 40	57	0.20 (0.20 to 0.27)	0.20 (0.20 to 0.89)*	0.20 (0.20 to 0.22)†
40 to 120	51	0.20 (0.20 to 0.40)	0.86 (0.20 to 6.00)*	0.20 (0.20 to 0.56)†
Access Numbers				
One	91	0.20 (0.20 to 0.30)	0.34 (0.20 to 1.35)*	0.20 (0.20 to 0.36)
Two	17	0.20 (0.20 to 0.23)	0.90 (0.28 to 6.15)*	0.20 (0.20 to 0.49)
Diabetes Mellitus				
Yes	5	0.70 (0.20 to 10.90)	2.20 (1.55 to 12.00)†	0.30 (0.20 to 11.50)†
No	103	0.20 (0.20 to 0.28)	0.36 (0.20 to 1.40)†	0.20 (0.20 to 0.36)†

Uβ2MG indicates urinary level of β-2 microglobulin.
*Uβ2MG change relative to pre-operative values was statistically significant in bivariable analysis between two subgroups of the factor under variables column ($P < .05$)
†Statistically significant difference in Uβ2MG between two subgroups of the factor under variables column in the analysis of covariance ($P < .05$)

Table 3. Risk factors for patients with normal pre-operative Uβ2MG who experienced high Uβ2MG on the 1st postoperative day

Characteristic	1st day Normal Uβ2MG N = 88	1st day High Uβ2MG N = 10	*P*
Gender, N (%)			
Male	60 (88)	8 (12)	NS
Female	28 (93)	2 (7)	
Stone size, cm, N (%)			
≤ 2	27 (90)	3 (10)	NS
> 2	61 (90)	7 (10)	
Pre-operative hydronephrosis, N (%)			
None to Mild	33 (92)	3 (8)	NS
Moderate to Severe	55 (89)	7 (11)	
Pre-operative kidney cortex, N (%)			
Thin	41 (89)	5 (11)	NS
Normal	47 (90)	5 (10)	
Operation duration, min, N (%)			
20 to 50	66 (99)	1 (1)	< .001
51 to 80	20 (74)	7 (26)	
81 to 120	2 (50)	2 (50)	
Access numbers, N (%)			
1	78 (96)	3 (4)	< .001
2	10 (59)	7 (41)	

NS indicates non-significant.

tubular injury in group N. The odds ratios (95% confidence interval) predicting the possibility of high postoperative Uβ2MG for pre-operative creatinine, pre-operative Uβ2MG, operation duration, and access numbers were 0.00 (0 to 0.64), 35.80 (1.11 to 11200), 1.07 (1.01 to 1.12), and 18.50 (2.7 to 120.3), respectively.

DISCUSSION

Early studies of PCNL that induced injury to the kidneys in animal models reported 1.5 ± 0.5% anatomic scar with no or minimal long-term functional changes.[2] Later human studies showed that this procedure does not result in impaired renal function.[1-3,5-7,14] However, there is the possibility of renal tubular injury after PCNL, but few studies have addressed this issue. Understanding the presence and importance of the kidney tubular injury during PCNL can provide further injury through medications or interventions like early re-PCNL.

Many studies have shown that Uβ2MG increases in renal tubular injury as an early marker;[8,12] therefore, it has been suggested as a screening tool for diagnosis of such injuries.[10] Urinary β-2 microglobulin has also been used to measure the kidney tubular injury after SWL.[15-17] An important point in using Uβ2MG as a renal injury assessment tool is its simple, non-invasive measurement, and the convenient serial tracking of its levels.[18]

Several human studies reported elevation of Uβ2MG in some conditions, such as obstructive pediatric and fetal uropathies, pediatric reflux disease,[19] heavy metal poisoning,[20,21] kidney trauma,[22] and spinal cord injuries.[23] One human study after PCNL reported increased levels of Uβ2MG that returned to normal level before one month.[24]

The results of this study suggest that pre-operative serum creatinine level plays a valuable predictive role in estimating PCNL-induced renal injury as pre-operative serum creatinine levels were correlated with postoperative changes of Uβ2MG on days 1 and 7. Urinary levels of β-2 microglobulin remained elevated and usually increased relative to their pre-operative values on the 7th day after the operation. High pre-operative serum creatinine level indicates prior kidney injury due to a chronic inflammatory process initiated by a renal stone.[25] These patients experienced further tubular injury during PCNL and its magnitude judged by Uβ2MG was higher than patients with normal pre-operative serum creatinine level.

In addition to pre-operative serum creatinine level, operation time was also associated with Uβ2MG changes on day 7. Operation time may result in more renal injury by factors, such as more prolonged litholapaxy, or indirectly through more complicated operations that prolong both operation duration and renal injuries.

In bivariable analysis, access numbers (one or two) were related to Uβ2MG changes on the 1st day, but not the 7th day. The same relationship was observed in group N. This finding has been previously reported by Eshghi and colleagues.[4] In their study on the kidney effects of PCNL measured by nuclear scans several weeks after the operation, no difference was noticed in cases of more than one nephrostomy tract creation compared with one tract creation. Increased access numbers can result in transient kidney injury that may be recovered soon.

Stone size was not a statistically significant predictor of postoperative Uβ2MG. We think that part of this observation is related to the narrow window of variability in the size of renal stones in this study, 95% of stones were 2 to 3.5 cm. Therefore, other factors, including stone composition, location, and caliceal anatomy could play more substantial roles in operation duration and tubular induced injury than stone size.

CONCLUSION

The findings of this study support the risk of renal tubular injury during PCNL, but shows that this injury may reverse before the 7th postoperative day in most patients. There is a subset of patients with high pre-operative serum creatinine level, presence of diabetes mellitus, or long operation time, in whom PCNL could result in a more prolonged injury.

CONFLICT OF INTEREST

None declared.

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