Smyrna Tıp Dergisi ***Araştırma Makalesi***

Effects of percutaneous nephrolithotomy operation on renal glomerular and proximal tubular functions

Perkütan nefrolitotomi ameliyatının renal glomerüler ve proksimal tübüler fonksiyonlar üzerine etkileri

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Summary
Objective: Aim of the study was to investigate the effects of percutaneous nephrolithotomy (PCNL) surgery on renal glomerular and proximal tubular functions.
Methods: Twenty-eight patients who underwent PCNL surgery due to renal stones were included in this study. All patients had the same characteristics regarding renal stone. Creatinine and β2-microglobulin levels were determined in the serum on preoperative day 1. and postoperative day 1., 3., 5. and 30.; and in the urine on postoperative day 1. Additionally, serum and urinary β2-microglobulin, creatinine clearance, β2-microglobulin clearance, renal tubular reabsorption rate of β2-microglobulin (TRβ2m) were also determined at the same intervals and the relationships between these were investigated.
Results: Preoperative and postoperative creatinine clearance, β2-microglobulin clearance, serum β2-microglobulin and urinary β2-microglobulin levels were not different ($p>0.05$). However, a significant negative correlation was observed between patient age and TRβ2m at first postoperative day 1 ($p<0.05$). No significant correlation was detected between patient age and operation time ($p>0.05$). Also, no significant relation was observed between TRβ2m and operation time, amount of liquid used and number of pneumatic lithotripsy pulses.
Conclusion: In conclusion PCNL surgery is a safe technique for renal stone treatment and do not cause any harmful influence on renal glomerüler and proximal tubular functions.
Key words: Renal stone disease, glomerular filtration rate, creatinine clearance, percutaneous nephrolithotomy, β2-microglobulin

Özet
Amaç: Bu çalışmanın amacı perkütan nefrolitotomi (PKNL) cerrahisinin renal glomerüler ve proksimal tübüler fonksiyonlar üzerindeki etkilerini araştırmaktır.
Gereç ve Yöntem: Böbrek taşı nedeniyle PKNL ameliyatı geçiren 28 hasta bu çalışmaya dahil edilmiştir. Tüm hastalar böbrek taşı açısından aynı özelliklere sahipti. Serum kreatinin ve β2-mikroglobulin düzeyleri, preoperatif 1. gün ve postoperatif 1., 3., 5. ve 30. günlerde ve idrar düzeyleri ise ameliyat sonrası 1. günde belirlenmiştir. Ek olarak, serum ve idrar β2-mikroglobulin, kreatinin klirensi, β2-mikroglobulin klirensi β2-mikroglobulinin (TRβ2m) renal tübüler reabsorbsiyon hızı da aynı aralıklarla belirlenmiş ve aralarındaki ilişkiler araştırılmıştır.
Bulgular: Preoperatif ve postoperatif kreatinin klirensi, β2-mikroglobulin klirensi, serum β2-mikroglobulin ve idrar β2-mikroglobulin düzeyleri arasında anlamlı fark bulunamamıştır ($p>0.05$). Ancak postoperatif 1. günde hasta yaşı ile TRβ2m arasında anlamlı negatif korelasyon gözlenmiştir ($p<0.05$). Hasta yaşı ile ameliyat süresi arasında anlamlı bir ilişki saptanmamıştır ($p>0.05$). Ayrıca TRβ2m ile operasyon süresi, kullanılan sıvı miktarı ve pnömatik litotripsi atım sayısı arasında anlamlı bir ilişki gözlemlenmemiştir.
Sonuç: Sonuç olarak, PKNL cerrahisi, renal taş tedavisi için güvenli bir tekniktir ve renal glomerüler ve proksimal tübüler fonksiyonlar üzerinde herhangi bir zararlı etkiye neden olmamaktadır.
Anahtar kelimeler: Böbrek taşı hastalığı, glomerüler filtrasyon hızı, kreatinin klirensi, perkütan nefrolitotomi, β2-mikroglobulin

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Introduction

The use of endoscopic management of renal stones can be considered as one of the biggest and most important developments in urology occurred in last 60 years. Since it was introduced in 1976 (1), percutaneous nephrolithotomy (PCNL) surgery has become one of the most common endoscopic procedures performed to remove the renal stones, especially large and complex ones (2,3,4).

The research about the success rate of PCNL, its complications and the degree of surgical trauma revealed that PCNL is a less invasive method compared to the other surgical methods (5,6,7,8). However, several reports indicated PCNL-associated postoperative complications such as colonic or pleural damage, pulmonary complications, septicaemia, renal haemorrhage (9,10,11). Moreover, PCNL has been suggested to be associated with renal trauma (12). Nevertheless, prospective studies comparing the extracorporeal shock wave lithotripsy (ESWL) method, which is one of the minimal invasive treatment options used in the to treat the renal stones, with PCNL, reported no significant difference between two methods in terms of kidney damage (6, 7, 13).

Various methods including measurement of serum creatinine levels, creatinine clearance (6, 14), urine levels of various biomarkers including kidney injury molecule-1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), N-acetyl-glucosaminidase (NAG) and liver-type fatty acid binding protein (LFABP) (15), nuclear imaging methods (16, 17) and β2-microglobulin (18). β2-microglobulin has been indicated to be a sensitive marker for evaluation of renal tubular damage and less affected by urinary obstruction (19), therefore, it possesses a good marker for evaluate the renal injury after PCNL.

In this study it was aimed to investigate the renal tubular injury and alterations in renal glomerular and proximal tubular functions in patients underwent PCNL.

Material and Methods

<u>*Patients*</u>
A total of 28 patients who underwent percutaneous nephrolithotomy (PNL) surgery for kidney stones at Inonu University Faculty of Medicine Urology Department between October 2003 and April 2004 were included in the study.

The patients between 18-75 years of age, without a disease affecting glomerular filtration rate such as analgesic nephropathy and renovascular hypertension, without the use of aminoglycoside, lithium and cyclosporin A, without a history of cancer of any type such as multiple myeloma, chronic lymphatic leukaemia and malignant melanoma, without a history of chronic inflammatory and autoimmune diseases such as systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), Sjogren's syndrome, without any other kind of kidney and blood diseases, without urinary system infection, and without disease or drug therapy that may affect kidney functions, and in the American Society of Anesthesiologists (ASA) risk score I were included in this study.

<u>*Preoperative investigations*</u>
Each patient underwent a thorough systemic examination before surgery and was examined for the presence of any systemic disease, kidney, heart and blood disease, or existing urinary tract infection and use of any medication. Preoperative routine urine cultures were obtained from all patients and presence of any infection was investigated. Those with infection were operated after treatment with appropriate antibiotics. Urine cultures of all patients were taken on the 1st, 3rd and 30th postoperative days, and examination for any infection was repeated. Preoperative premedication, anaesthesia and surgical method performed on all patients were the same as standard.

<u>*Surgical procedure*</u>
Previous to the surgery, Patients received diazem (10 mg, orally) on the night and on operation day and famotidine (40 mg, orally), on the night previous night as premedication. Anaesthesia was induced by intravenous administration of 2% lidocaine (1 mg/kg), thiopental sodium (5 mg/kg), vecuronium bromide (0.1 mg/kg) and alfentanil (10 μg/kg).

Anaesthesia maintenance was achieved by N_2O:O_2 (50%/50%) and isoflurane (1-5%/ volume) administration via inhalation. During the surgery, respiration rate, heart rate, oxygen saturation, peripheral blood pressure and tidal volume of the patients were monitored. Tidal volume of the patients was kept at 8 mL/kg under anaesthesia.

Following anaesthesia induction, patients were installed in lithotomy position, bladder was accessed by using a 22 Fr cystoscope (Karl Storz SE & Co., Germany) and an endovision set (Telecam SL camera, Karl Storz SE & Co., Germany; Xenon 300 Cold Light Fountain, Karl Storz SE & Co., Germany; Sony Color Pal-

Secam monitor, The Sony Corp., Japan), the pelvic urethral stone was detected and a 6 Fr urethral catheter (90 cm; Microvasive-Boston Scientific-Boston) was placed in the renal pelvis. Catheter was then stabilized by silk sutures after placing an 18 Fr Foley catheter into urethra. During this procedure , patients were stabilized in prone position and supported with silicon pillows under the chest to improve mechanical ventilation. The surgical area then was disinfected with 10% povidone iodide.

Renal stone was detected by a portable fluoroscope (Shimadzu Opescope LGD, Shimadzu Corp, Japan). The most optimal renal calyx to approach the renal stone was determined by injection of contrast agent (meglumine + amidotrizoate) and an access was achieved by using a percutaneus access needle (18 Gauge-Microvasive, Boston Scieııtific, USA). A guide wire (Amplatz Guidewire, 0.038-inch, J type; Microvasive, Boston Scientific, USA) was proceeded to urethra through the access needle, access needle was removed, and a 1-cm long skin incision was performed. A nephrostomy access was achieved by moving the dilator set accessories (Amplatz Renal Dilator Set, Microvasive, Boston Scientific, USA) on the guide wire up to 30 Fr (1 cm) before calyx, a second guide wire was placed near the first guide wire as a “security wire” and a renal sheath (Amplatz Renal Sheat 34FrX17 cm, Microvasive, Boston Scientific, USA) was placed to maintain the nephrostomy access clear. Intrarenal imagin was conducted by using an Alken-Hohenfellner nephroscope (Karl Storz SE & Co., Germany) and endovision set that was mentioned before. The continuous irrigation for imaging was provided with isotonic NaCl solution at 37 ºC. The renal stones detected by fluoroscope and nephroscope were removed by using grasping forceps (Karl Storz SE & Co., Germany) in case the stones were small enough to pass through the renal sheath. If the diameter of the stones were bigger than 1 cm, they were removed by using grasping forceps after destroyed by PCNL (6 atm, 400 bpm; PCK Calculith 20/60hZ, PCK-Ankara, Turkey). Stone remaining with a diameter of 2 mm or less were aspirated with an 18 Fr nelaton catheter.

After confirmation of the renal stone treatment with fluoroscope and nephroscope, a 22 Fr Foley catheter were placed in the renal calyx as nephrostomy, the catheter was stabilized on the skin with silk sutures and a contrast agent was infused in the calyx to confirm the placement of the catheter. After the confirmation of the catheter, renal sheath and both guide wires were removed, and surgical procedure was terminated.

<u>Biochemical analysis</u>

In order to investigate the renal proximal tubular injury serum and urinary β2-microglobulin levels were analysed.

For the analyses of serum β2-microglobulin levels, preoperative, postoperative day 1, 3, 5 and 30 blood samples were collected and for the urinary levels of β2-microglobulin, postoperative 24 h urine samples were collected. The blood samples were kept at room temperature for 1 h and then centrifuged at 3,000 rpm for 15 min. Then serum was collected and stored at -20ºC until the analysis. For the urine samples, the volume of total urine were calculated and pH of the urine was set above 6 to prevent the degradation of urinary β2-microglobulin (20, 21). Then the urinary samples were centrifuged at 3,000 rpm, 3 mL of the supernatant was collected and stored at -20ºC until the analysis. Serum and urine samples were then thawed at room temperature and β2-microglobulin levels were determined on a nephelometer (Behring Nephelometer 100 Analyzer, Germany). Thrombocyte (Trb), white blood cell (WBC) and haemoglobin (Hb) levels (Beckman Coulter LH750 Analyzer, USA) and blood biochemistry parameters including blood urea nitrogen (BUN), creatinine (Cr), sodium (Na^+), potassium (K^+), chloride (Cl^-) and calcium (Ca^+) levels were measured (Olympus AU 600).

Variations in glomerular filtration rate (GFR) were investigated by analysing the Cr clearance (C_{Cr}). β2-microglobulin clearance (Cβ2m) of the patients were calculated by using the serum and urinary β2-microglobulin (Sβ2m and Uβ2m, respectively) levels by using Equation 1 (20, 22). After calculating endogenous Cr clearance and β2-microglobulin clearance tubular reabsorption rate of β2-microglobulin (TRβ2m) was calculated Equation 2 (20, 22).

$$C\beta 2m = \frac{(U\beta 2m \times 24\ h\ urinary\ volume\ (mL))}{(S\beta 2m \times duration\ of\ urinary\ collection\ (min))} \qquad \text{(Equation 1)}$$

$$TR\beta 2m\ (\%) = (1 - \left(\frac{C\beta 2m}{C_{Cr}}\right) \times 100 \qquad \text{(Equation 2)}$$

Age and stone burden of the patients, side that the renal stone was located, duration of the surgery, number of pneumatic pulses, amount of liquid used, additional medication during the surgery, type of anaesthesia and surgical complications were recorded.

Statistical Analysis

Data were represented as minimum, maximum, frequency and mean ± standard deviation (SD). By considering the number of patients, non-parametric tests for the correlation tests, Friedman test and Pearson's correlation coefficient, were used for the statistical analyses. A p value lower than 0.05 was considered as statistically significant.

Results

Most of the patients included in the study were male (Table 1). Mean age of the patients was 44.4±12.4 years. Mean size of the renal stone burden was 476.7±384.8 mm^2 and mean duration of the surgery was 130.5±67.4 min (Table 1). The liquid required during the surgery ranged between 2-45 L (Table 1). Fifteen (53.5%) and 13 (46.5%) of the patients had renal stones in the left and the right kidney, respectively. The number of pneumatic pulses ranged between 0 and 3630 bpm (Table 1) and in six of the patients (21.4%), no pneumatic pulses were required. Only in one patient, renal access was achieved by double puncture with the access needle while in the rest of the patients, renal access could be achieved with single puncture.

Table 1. *General characteristics of the patients*

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Gender	**(n (%))**
Male	20 (71.4)
Female	8 (28.6)
Age (mean ± SD / min - max)	44.4 ± 12.4 / 22 – 77
Renal stone burden (mm^2 / min - max)	476.7 ± 384.8 / 80 – 1500
Duration of the surgery (min; mean ± SD / min - max)	130.5 ± 67.4 / 40 – 280
Location of the surgery (n (%))	
Left	15 (53.5)
Right	13 (46.5)
Number of pneumatic bets (mean ± SD / min - max)	554.3 ± 748.0 / 0 – 3630

There were no significant differences in preoperative, postoperative day 1, 3, 5 and 30 C_{Cr}, in another terms, GFR, values between the groups (p>0.05; Table 2). Moreover, no significant differences in preoperative, postoperative day 1, 3, 5 and 30 Sβ2m and Uβ2m levels (p>0.05; Table 2). Similarly, there was no significant differences in preoperative, postoperative day 1, 3, 5 and 30 Cβ2m values between the groups (p>0.05; Table 2). On the other hand, there were no significant differences in in preoperative, postoperative day 1, 3, 5 and 30 TRβ2m values between the groups (p>0.05; Table 2).

Table 2. *Preoperative, postoperative day 1, 3, 5 and 30 C_{Cr}, Sβ2m, Uβ2m, Cβ2m, TRβ2m values of the patients*

		Postoperative day (Mean ± SD (min - max)				P
	Preoperative	**1**	**3**	**5**	**30**	
C_{Cr}	138.9 ± 73.1 (25.5 - 315)	104.7 ± 53.1 (47.7 - 266)	143.5 ± 81.3 (33.8 - 357)	136.1 ± 65.5 (39 - 278.6)	150.0 ± 64.8 (44.8 - 352)	0.177
Sβ2m	384.3 ± 14.0 (362 - 422)	383.4 ± 10.7 (362 - 408)	382.3 ± 14.6 (357 - 414)	382.9 ± 14.9 (363 - 421)	380.7 ± 12.4 (361 - 409)	0.749
Uβ2m	384.0 ± 17.7 (360 - 425)	378.2 ± 10.0 (357 - 397)	379.8 ± 9.7 (361 - 402)	380.2 ± 11.9 (361 - 410)	1.78 ± 0.43 (1.08 - 2.63)	0.746
Cβ2m	1.56 ± 0.42 (0.75 - 2.36)	1.73 ± 0.51 (0.80 - 2.74)	2.14 ± 0.80 (0.90 - 4.13)	1.98 ± 0.65 (0.85 - 3.55)	1.78 ± 0.43 (1.08 - 2.63)	0.022
TRβ2m	98.3 ± 1.3 (93.6 - 99.9)	98.1 ± 0.80 (96.2 - 99.7)	98.1 ± 0.97 (96.1 - 99.3)	98.3 ± 0.97 (94.8 - 99.4)	98.5 ± 0.57 (97 - 99.3)	0.059

Statistical analysis: Friedman Test

Correlation analyses revealed a significant negative correlation between the age of the patient and TRβ2m values on postoperative day 1 ($p<0.05$), however, this correlation disappeared on the other days ($p>0.05$; Table 3). On the other hand, there were no significant correlations were observed between TRβ2m values and number pneumatic pulses, amount of liquid used or duration of the surgery ($p>0.05$; Table 3).

Table 3. *Correlations between TRβ2m values and age, duration of the surgery, amount of liquid or number of pneumatic pulses*

		Postoperative day (Pearson's r)			
	Preoperative	**1**	**3**	**5**	**30**
Age	-0.191	**-0.452***	-0.296	0.001	-0.221
Duration of the surgery	-0.325	0.089	-0.330	-0.142	-0.362
Amount of liquid	-0,276	0.051	-0.223	-0.082	-0.331
Number of pneumatic pulses	-0.253	0.143	-0.96	-0.92	-0.285

** p<0.05*

Discussion

Due to its recurrent nature, renal stone disease is an important problem for both the patient and the physician. While dealing with this disease, which has no definite treatment yet, the physician should explain to the patients and their relatives that the disease may recur in the following years and require re-treatment, regardless of the initial treatment method and success (1,23,24). While planning both the first treatment and the recurrence treatment for stone disease, the physician should carefully calculate the damage that the treatment method may cause on the kidney, and accordingly, select and perform the treatment that will cause the least damage. This necessitates the researchers to continually seek less invasive treatment methods. PCNL surgery has also emerged as a result of these studies.

Since the first clinical application in 1976, many studies have been carried out to investigate how invasive PCNL actually is and these studies mainly focused on renal function after PCNL surgery. In a study by Liou et al., long-term renal tissue damage was examined and no significant change in GFR and serum Cr levels after two years of follow-up period was observed (13). There are publications suggesting that the first surgical procedure should be PCNL, especially in children, considering the risk of having multiple surgical procedures due to recurrent renal stone disease (25,26,27,28). In the presented study, it was aimed to investigate the changes in renal glomeruli and proximal tubule function that occur in patients who underwent PCNL prospectively by biochemical monitoring of β2-microglobulin levels peripheral blood and urine samples.

A negative correlation was observed between patient age and TRβ2m only on the first postoperative day. The decrease in glomerular filtration rate and proximal tubule functions is a result of aging, and it is acceptable for these elderly patients to take more time to recover from trauma compared to younger patients. On the other hand, there was no significant correlation between the age of the patients and TRβ2m values on the other postoperative days. In separate studies conducted by Musialik (20) and Schardijn et al. (29) , it was reported that urinary β2-microglobulin excretion was similar in healthy subjects and patients with active metabolic stone disease. In addition, Musialik compared the patients with active metabolic stone disease and those without chronic pyelonephritis (20). Serum and urinary β2-microglobulin levels were found to be high in those with pyelonephritis and normal in those without pyelonephritis (20). In the same study, the TRβ2m rate was also found to be low in those with pyelonephritis (20). In the presented study, no chronic pyelonephritis was detected in any of the patients, and preoperative serum and urinary β2-microglobulin values and, accordingly, the TRβ2m ratio were found to be normal values, due to the absence of active urinary infection.

Since serum and urinary β2-microglobulin values are independent of body weight and gender, β2-microglobulin clearance is more sensitive than Cr clearance in the evaluation of renal functions and calculation of glomerular filtration rate (22,30,31,32,33). It is reported that β2-microglobulin is the earliest and most sensitive precursor of changes in kidney function after transplantation and is also used routinely (29,31). In the performed study, it was observed that there was no significant change in β2-microglobulin clearance between preoperative and postoperative days, and it was observed to be in parallel with creatinine clearance and no significant relationship between the degree of proximal tubule damage caused by variables and TRβ2m was observed. Here, the most important variable in terms of proximal tubule damage should be expected as the mechanical trauma caused by pneumatic impact. However, the pneumatic pulse is not in contact with the renal parenchyma and is usually performed on the stone surface in the renal pelvis within the renal collecting system. In this respect, it is natural that the pneumatic pulse has no effect on the renal parenchyma, thus renal glomerular and proximal tubule functions.

In the study of Wilson et al. comparing ESWL, PNL, and open kidney surgery on an animal model, they reported that the only group with kidney scarring was the PNL group (6). Histological damage to the renal parenchyma is inevitable during the gradual dilatation and placement of the percutaneous nephrostomy tube by entering the appropriate calyx with the percutaneous insertion needle, which constitutes the most important part of PNL surgery. However, as stated in the study of Wilson et al., the scar tissue caused by this maximal damage is much less than 2% of the total treated volume of the kidney (6,34). Therefore, PNL surgery does not cause any change in glomerular and proximal tubule functions. However, it is difficult to express an opinion about the scarring in our patient group, since we did not conduct a research that could evaluate renal scarring in our study.

Conclusion

PCNL surgery, that it is a minimally invasive technique for the kidney did not cause a significant change in renal endogenous Cr clearance and β2-microglobulin clearance and after PCNL surgery, serum and urinary β2-microglobulin levels and the rate of tubular reabsorption of β2-microglobulin did not show a significant change compared to the preoperative period. At the same time, these values were not affected by patient and surgery variables. Therefore, in conclusion our results suggest that PCNL surgery has no damaging effect on renal glomerular and proximal tubular functions.

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