

COMPARISON OF SERUM KIM-1 AND MIOX LEVELS IN PATIENTS THAT UNDERWENT PERCUTANEOUS NEPHROLITHOTOMY AND FLEXIBLE URETERORENOSCOPY

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Abstract

Aim: Percutaneous nephrolithotomy (PNL) and retrograde intrarenal surgery (RIRS) are common surgical methods in the treatment of kidney stones. Possible effects on kidneys are an important factor in determining the surgical procedure and the surgical method. In our study, kidney injury molecule-1 (KIM-1) and myo-inositol oxygenase (MIOX) were used to compare acute kidney injury in patients that underwent PNL and RIRS. **Material and Method:** Eighty patients aged 20 to 75, who underwent PNL or RIRS in our urology clinic between November 2018 and February 2020 were included in the study. In this prospective study, the demographic characteristics, stone size, operation time, preoperative and postoperative hemoglobin and biochemistry values of the patients were recorded. 5 cc blood samples taken from the patients before the operation and at the fourth hour after the operation were centrifuged and kept at -80 °C, and the KIM-1 and MIOX levels were measured in the biochemistry department. **Results:** There was no difference between the groups in terms of demographic data; however, the operation time and length of hospital stay were significantly longer in the PNL group. The mean increase in MIOX was 10.583±9.73 ng/ml and 7.501±16.46 ng/ml in the PNL and RIRS groups, respectively. Although there was a statistically significant increase in both groups, this increase was greater in the PNL group. A significant increase was observed only in the PNL group in the postoperative period (p=0.003). **Discussion and Conclusion:** The findings of the study suggest that the PNL procedure causes more damage to the kidneys than RIRS.

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Discussion and Conclusion: The findings of the study suggest that the PNL procedure causes more damage to the kidneys than RIRS.

What's already known about this topic?

PNL and RIRS are common surgical methods. It is known that surgical procedures for kidney stones may have negative effects on kidneys.

What does this article add?

Serum kim-1 and miox molecules were used for the first time in patients treated with PNL and RIRS. It has been demonstrated with these molecules that PNL does more damage than RIRS.

INTRODUCTION

Kidney stone disease is one of the most common urinary system diseases. It has a recurrence rate of up to 50% within five years [1]. Different treatment methods are available in patients with kidney stones according to the size and location of the stone. There are treatment alternatives in kidney stones, such as stone fragmentation with extracorporeal shock wave lithotripsy (ESWL), percutaneous nephrolithotomy (PNL), and retrograde intrarenal surgery (RIRS). PNL is a method of removing stones by first fragmenting them with lithotriptors after percutaneous entry into the kidney. Percutaneous access to the kidney was first reported in 1955 by Goodwin et al., and the first PNL procedure was described by Fernström in 1976 as a treatment option for kidney stones [2; 3]. However, with the introduction of ESWL in the early 1980s, the use of PNL has decreased but it can be an appropriate treatment method, especially for treating large or multiple kidney stones and stones located in the lower calyx [4]. The European Association of Urology (EAU) guidelines also recommend PNL as the first option in the treatment of kidney stones larger than 2 cm [5]. RIRS is the name given to the process of fragmenting the stone with a laser accessing the kidney through the ureter with a flexible ureterorenoscope. This technique has the advantages of using natural methods and patients requiring shorter hospital stay in the postoperative period. The success of RIRS is related to the size, hardness and location of the stone [6].

When kidney functions are impaired, blood urea and creatinine levels increase, but this may occur hours, even days later. Some markers are used in urine and blood to detect kidney dysfunction earlier. Among the markers that have been shown to be effective in determining kidney damage are some urinary enzymes [7], cystatin C, urine cytokines; myo-inositol oxygenase (MIOX), and kidney damage molecules [e.g., kidney injury molecule-1 (KIM-1)] [8; 9].

Although there is no specific blood marker showing kidney damage, KIM-1 is released at high rates in proximal tubular cells after this damage. Although KIM-1 is mostly used as a urine marker for kidney damage, it has been revealed that it can also be detected in the blood to detect kidney injury [10; 11].

Gaut et al. used the Western blot technique and reported that the increase in myo-inositol oxygenase (MIOX), which has been demonstrated to be specific to proximal renal tubules, occurred approximately two days before the increase in the serum creatinine level in kidney damage, and therefore it can be used as a potential early diagnosis sign for acute kidney injury [12].

In this study, we aimed to reveal the possible acute kidney damage caused by these surgical techniques by measuring plasma KIM-1 and MIOX levels at the preoperative and postoperative fourth hour in patients who underwent PNL and RIRS, and to compare these two techniques in terms of these parameters.

MATERIAL AND METHOD

This study was conducted at the urology clinic of Erzincan Binali Yıldırım University between November 15, 2018 and February 15, 2020 in accordance with the principles of the Declaration of Helsinki, patient rights regulation and ethical rules, after receiving the ethics committee approval (numbered 33216249_604.01.02.E.49628, dated November 9, 2018). Eighty patients scheduled for PNL or RIRS in our urology clinic were included in the study. The patients were informed about the study in advance, and their consent was obtained for participation in the study.

The patients' age, gender, operation time, operation side, stone location, stone size, kidney entry points (in the PNL group), presence of postoperative residual stones, and length of hospital stay were recorded. Three patients were excluded from the study due to solitary kidney, 4 due to renal dysfunction, 1 due to skeletal deformity (scoliosis), and 1 due to ectopic kidney.

Preoperative complete blood count analysis, serum urea analysis, biochemical tests containing creatinine and blood parameters, posterior-anterior chest radiography, ECG, serological tests, and urine culture analysis were performed in all patients. In the postoperative period, complete blood count and urea creatinine values were examined again. In order to reveal the presence of residual stones, non-contrast computed tomography was performed one month after the operation, and stones smaller than 4 mm were accepted as clinically insignificant residual fragments (CIRFs). Complete stone-free status and CIRFs were considered to indicate operative success. The Clavien classification was used to evaluate the complications that developed.

Venous blood samples were taken preoperatively and four hours after the operation from each patient who underwent surgery in our service and were included in the study. These samples were centrifuged and stored at -80 °C.

Rirs Technique

The patients in this group were placed in the lithotomy position, and a semirigid ureteroscope (Karl Storz 9-11F, Tuttlingen, Germany), followed by a9.5-11-F access sheath (Boston Scientific, USA) were inserted with a through a sensor guide (PTFE-Nitinol Guidewire with Hydrophilic Tip, Boston Scientific, Marlborough, USA) under fluoroscopy control. The stone was accessed using a flexible ureteroscope (7,95 F Olympus, USA), and fragmentation was performed using Holmium YAG laser with 272-µm laser fibers (Quanta System, Litho Holmium, YAG Laser, Turkey). Large fragments were extracted using a 1.7 F retrieval basket (Zerotip, Boston Scientific Corp, Natick, MA, USA).

Pnl Technique

The patients were placed in the lithotomy position, and following the insertion of a semirigid ureteroscope (Karl Storz 9-11F, Tuttlingen, Germany) and a sensor guide (PTFE-Nitinol Guidewire with Hydrophilic Tip, Boston Scientific, Marlborough, USA) an open-ended ureteral catheter was placed under fluoroscopy guidance. After placing the patients in the prone position, retrograde pyelography was performed, and a percutaneous insertion needle was inserted into the appropriate calyx. Under guidance, 28-F Amplatz dilatation (Geotec, Ankara, Turkey) was applied to all patients. Stones were reached using a nephroscope (Karl Storz 26F, Germany), and the stones were fragmented with pneumatic lithotripsy (Elmed, Vibrolith Plus, Turkey). The fragmented pieces were removed from the kidney with stone forceps. A 14-F or 16-F nephrostomy tube was placed in all patients. After fluoroscopy control, antegrade pyelography was performed, and the procedure was terminated.

Statistical analysis

Data were analyzed using SPSS version 25.0 (SPSS®, IL, USA). The compliance of the data with the normal distribution curve was evaluated using the Shapiro-Wilk test. Continuous variables were compared using Student's t-test and Mann-Whitney U test, and categorical data were compared using the chi-square test. For the comparison of the preoperative and postoperative data within the groups, the t-test and Wilcoxon test were used in dependent groups. $P < 0.05$ was considered statistically significant.

RESULTS

In this prospectively conducted study, no difference was observed between the groups in terms of the mean age, female/male ratio, BMI, presence of DM and stone locations. However, the mean stone dimensions were calculated as $343.65 \pm 236.63 \text{ mm}^2$ and $122.48 \pm 51.292 \text{ mm}^2$ for the PNL and RIRS groups, respectively, indicating a statistically significant difference ($p [?] 0.001$) (Table1).

The mean operation time of the patients was 60.25 ± 22.98 and 47.50 ± 20.69 minutes in the PNL and RIRS groups, respectively, and a statistically significant difference was found between the two groups ($p [?] 0.001$). The mean length of hospital stay was 4.10 ± 2.37 days in the PNL arm and 1.53 ± 1.61 days in the RIRS arm, also indicating a statistically significant difference ($p [?] 0.001$). Stone-free status and presence of CIRFs were accepted as surgical success, and there was no statistically significant difference between the two groups in terms of this outcome. The modified Clavien classification was used for the postoperative complication evaluation. Twenty-six patients (65%) that had undergone RIRS were evaluated as Clavien 0, 12 (30%) patients as Clavien 1, and 2 (5%) patients as Clavien 2 (infection) (22.5%). In the PNL group, Clavien 0 was seen in 9 (22.5%) patients, Clavien 2 in 6 (22.5%) (infection in 4, bleeding in 1, and arteriovenous fistula in 1), and Clavien 3A in 1 (2.5%) (double-J stent requirement). There was a statistically significant difference between the two groups in terms of the Clavien classification ($p=0.001$) (Table1).

Preoperative hemoglobin, urea, creatinine, GFR, MIOX and KIM-1 levels, no significant difference was observed between two groups. In the PNL arm, the post-operative hemoglobin ($12.92 \pm 1.37 \text{ g/dl}$) was found to be statistically significantly lower than in the RIRS arm ($14.98 \pm 3.30 \text{ g/dl}$) ($p [?] 0.001$) (Table 2).

In the intra-group comparisons, there was no statistically significant difference between the preoperative and postoperative values of hemoglobin urea, creatinine, GFR and KIM-1 in patients that had undergone RIRS; however, the mean MIOX value was increased from $17.80 \pm 15.39 \text{ ng/ml}$ preoperatively to $25.30 \pm 20.11 \text{ ng/ml}$ postoperative, and this increase was statistically significant ($p = 0.001$) (Table 2). Within the PNL group, the hemoglobin value was measured as $14.01 \pm 1.34 \text{ mg/dl}$ preoperatively and $12.92 \pm 1.37 \text{ mg/dl}$ postoperatively, indicating a statistically significant difference ($p [?] 0.001$). Similarly, in this group, the preoperative and postoperative KIM-1 values were 1.21 ± 0.44 and $1.68 \pm 0.58 \text{ ng/ml}$, respectively, and the preoperative and postoperative MIOX values were $15.23 \pm 9.36 \text{ ng/ml}$ and $25.81 \pm 16.13 \text{ ng/ml}$, respectively showing a statistically significant difference ($p [?] 0.001$ for both). No significant difference was observed in terms of the other variables (Table 2). In the intra-group evaluation for the postoperative and preoperative differences, the mean MIOX increase was calculated as $7.501 \pm 16.46 \text{ ng/ml}$ for the RIRS group and $10.583 \pm 9.73 \text{ ng/ml}$ in the PNL group, and there a statistically significant difference between the two groups in favor of the latter ($p = 0.001$). Similarly, while the mean KIM-1 increase was $0.375 \pm 1.13 \text{ ng/ml}$ in the RIRS group, it was $0.471 \pm 0.328 \text{ ng/ml}$ in the PNL group, indicating a statistically significant difference ($p = 0.003$) (Table 2).

DISCUSSION

Urinary system stone disease is a pathology that constitutes an important part of urology practice. The treatment of kidney stone disease has changed significantly, especially in the last two decades, with the improvement of tools and reduction in their size due to the development of technology. ESWL, PNL and RIRS are considered as three main treatment methods for the treatment of upper urinary stone disease [13].

PNL is recommended as the preferred minimally invasive method due to its high success rates in patients with a high stone burden ($>20 \text{ mm}$) and complex stones [5]. However, complications, such as hemodynamic impairment, vascular bleeding, and parenchymal bleeding, and acute kidney injury may occur after the operation [14]. In recent years, with the technological advances in endourological equipment and increasing surgeon experience, RIRS presents as an alternative to PNL, with lower complication rates [15; 16]. There are publications that consider RIRS to be a very good minimally invasive treatment alternative for intrarenal stones of $<20 \text{ mm}$ and report high stone-free rates even in larger stone sizes [17; 18].

During surgical operations for kidney stones, there may be certain damage to the kidneys. Having knowledge of the extent of injury caused by each technique used can guide surgeons in the selection of both patients and surgical techniques. Creatinine is used in daily practice to show kidney injury. However, creatinine is a non-specific marker affected by various factors, including age, gender, muscle density, and liver function. In addition, creatinine levels increase days after kidney damage occurs by which time 50% or more of renal function is lost [19]. Therefore, new molecules have been used to reveal kidney injury more specifically at an earlier stage. In an experimental animal model investigating one of these molecules, KIM-1, the urine and plasma levels were measured after inducing ischemic kidney injury. It was found that the plasma KIM-1 significantly increased at the third hour compared to the preoperative levels and remained at a high level until the 96th hour [20]. In the same study, it was shown that the plasma KIM-1 level was correlated with urine the KIM-1 level and significantly higher in individuals with kidney injury compared to healthy individuals. Many studies have evaluated urine KIM-1 levels; however, to the best of our knowledge, there is no study in the literature investigating the role of plasma KIM-1 molecule in revealing possible damage of kidney stone surgery.

In a previous study, the diagnostic sensitivity and specificity of the MIOX molecule released from the proximal tubules of kidneys in showing acute kidney injury were observed as 53.8% and 81.5%, respectively. Accordingly, it was concluded that MIOX could be used as a marker of acute kidney injury [21]. In addition, when compared to creatinine, MIOX was observed to increase much earlier in case of kidney injury [21]. However, a review of the literature shows no study comparing the MIOX molecule in patients that have undergone PNL and RIRS.

In our study, the stone volume of the PNL group was statistically significantly higher than that of the RIRS group ($p < 0.001$). This difference was due to the indication of PNL for stones with a larger volume, as recommended in the EAU 2019 urinary system stone disease guidelines. In addition, the operation time was significantly longer in the PNL group (60.25 \pm 22.98 min) compared to the RIRS group (47.50 \pm 20.69 min) (p [?] 0.001). We also consider this to be related to the different stone volumes. Similarly, in other studies comparing PNL and RIRS, the stone volume was observed to be higher and the operation time was longer operation times in the former [13; 22]. However, in a study in which the stone sizes were similar in the two surgery groups, the RIRS duration was found to be longer in lower pole stones [23]. The main reason for the prolongation of this period may be due to the more difficult manipulation of the flexible ureteroscope in lower pole stones. In our study, the length of hospital stay was 4.10 \pm 2.37 days in the PNL group and 1.53 \pm 1.61 days in the RIRS group, indicating a statistically significantly longer value for the former (p [?] 0.001), which is consistent with the literature [13; 22; 23].

In this study, the operative success rates were 92.5% and 90% in the PNL and RIRS arms, respectively, and no statistical difference was observed between them. The success rates of the studies in the literature were also similar. However, the postoperative stone-free rates are affected by clinical parameters, such as stone location, obesity, stone size, stone composition and anatomy of the renal calyces. There are studies reporting 77% to >90% success rates in RIRS whereas for PNL, the success rates for lower pole stones of 1-2 cm and above 2 cm are given as 92% and 86%, respectively [25]. While two studies [26; 27] showed a higher stone-free rate in the PNL group (92 and 98%, respectively) than the RIRS group (89 and 95%, respectively), another study showed a statistically non-significant higher stone-free rate in the RIRS group compared to the PNL group [28]. Lastly, Mehmet et al. determined the stone-free rates as 91.4% and 87% in the PNL and RIRS groups, respectively [13].

We used the modified Clavien classification to evaluate the complications and found the rate of complications to be statistically significantly higher in the PNL arm ($p = 0.001$). Similar to our results, the literature contains studies indicating a higher rate of complications in the PNL arm than in the RIRS arm [23; 28]. While no major complications were observed in our study, 2 (5%) patients in the PNL arm required blood transfusion. Post-operative fever occurred in 7 patients (17.5%) in the PNL arm and 2 (5%) patients in the RIRS arm.

In a review reported the most common complications of PNL as extravasation (7.2%), bleeding requiring

blood transfusion (11.2 - 17.5%), and fever (21 - 32.1%) while rare major complications included septicemia (0.3 - 4.7%), colon injury (0.2 - 4.8%), and pleural injury (0 - 3.1%) (24).

In our study, while there was no difference between the preoperative and postoperative hemoglobin values in the RIRS arm, the postoperative hemoglobin was statistically significant lower compared to the preoperative value in the PNL arm (p [?] 0.001). GyooHwan Jung et al. reported similar data to our results.

In a previous study conducted with RIRS patients, it was observed that MIOX did not increase in the postoperative period [29]. In contrast, the postoperative values of the MIOX molecule statistically significantly increased in our PNL group. The preoperative and postoperative MIOX levels in the RIRS arm were 17.80 ± 15.3 and 25.30 ± 20.11 ng/ml, respectively, and we found a statistically significant increase in this parameter ($p = 0.001$). However, the increase in the MIOX values was 10.583 ± 9.73 ng/ml in the PNL group versus 7.501 ± 16.46 ng/ml in the RIRS arm, indicating a statistically significantly higher increase in the former ($p = 0.001$) (Table 2).

In this study, although there was an increase in the plasma KIM-1 levels in the RIRS arm in the postoperative period, no statistically significant difference was observed. However, the postoperative KIM-1 value in the PNL arm was found to be statistically significantly higher than the preoperative value. Our findings are supported by Balasar et al.[30], who compared PNL, RIRS and mini-PNL, and found an increase in the KIM-1/creatinine values in the PNL and RIRS arms in the postoperative period, and this increase was statistically significantly higher in the PNL group.

We detected a statistically significant increase in both the KIM-1 and MIOX values in the postoperative period among the patients that had undergone PNL. In the RIRS group, this increase was observed only in MIOX. We showed that acute kidney injury occurred in both surgical methods; however, it was greater in PNL.

Limitations

The limitations of this study include the relatively low number of the patients in our sample and a single blood sample collection in the postoperative period.

CONCLUSION

In the comparison of the patients that underwent PNL or RIRS, we first demonstrated that acute kidney injury could be detected using the MIOX and plasma KIM-1 molecules, and the increase in these molecules was higher in the PNL arm. The higher increase in the PNL arm suggests that this method causes greater acute kidney injury than RIRS; however, there is a need for further studies with larger case series to support our data.

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