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Investigation of urinary neutrophil gelatinase associated lipocalin (NGAL) for early diagnosis of acute kidney injury after percutaneous nephrolithotomy

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Percutaneous;
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Kidney stones

Abstract

Introduction: Percutaneous nephrolithotomy (PCNL) could be mentioned as the most important treatment of choice for kidney staghorn stones. Previous publications reported that the novel biomarker urinary neutrophil gelatinase-associated lipocalin (NGAL) activity significantly increases in acute kidney injury (AKI) but there is not many published articles related to increase of NGAL after PCNL procedure.

Objective: This study aimed to investigate AKI by urinary measurement of NGAL after PCNL procedure.

Subjects and methods: Based on a cross-sectional design, 41 patients with staghorn renal stones were nominated. All patients have been informed and signed the consent form. NGAL levels were measured by urinary sampling at 2 h before and 12 h after the procedure. Serum creatinines (Cr) were measured 12 h before and 48 h after the surgery. Demographic and clinical data including surgical procedure were recorded in Excel and analyzed by SPSS (SPSS Inc., Chicago, IL) for windows.

Results: With a minimum of 20 and a maximum of 70, the mean age of patients was 47 years old. 71% of patients studied were males. There was a significant change in mean serum Cr (1.06 versus 1.12 mg/dL; $p < 0.01$) before and after the procedure respectively. Glomerular filtration rate (GFR) with a mean of 81.93 umol/L before the procedure was decreased ($p < 0.02$) to 77.46 umol/L after the procedure. The changes in urine level of NGAL were significant ($p < 0.02$), associated to an increase in mean value of 20.63 ng/mL (two hours before) versus 56.28 ng/mL (twelve hours after)the PCNL procedure.

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Conclusions: Within different extents after PCNL procedure there was a significant increase in the biomarker of NGAL levels.In order to reduce AKI and other post-operative complications, further studies in a large population of patients seem to be advantageous.

Introduction

The 25-kDa lipocalin-2 (LCN2) or oncogene 24p3 or neutrophil gelatinase-associated lipocalin (NGAL) first recognized as a protein accumulated in particular granules of the human neutrophil and encoded by the LCN2 gene. The protein is supposed to attach small lipophilc substances such as bacterial resultant formyl peptides and lipopolysaccharides (LPS) and might function as a modulator of inflammation [1]. Upon encountering attacking bacteria the toll-like receptors on immune cells motivate the synthesis and secretion of NGAL. Secreted NGAL then limits bacterial growth that is involved in the intrinsic immunity responses by sequestrating iron that in turn restricted bacterial growth by binding to bacterial siderophores. It is articulated in neutrophils and in low levels in the kidney, prostate and epithelia of the respiratory and alimentary tracts. There are many investigations that confirm NGAL could be used as a biomarker of kidney injuries due to stones or other related disorders [2,3]. Precutaneous kidney surgery reported to be as routine management related to a number of kidney pathologies [4–6]. Previous publication confirmed that percutaneous nephrolithotomy (PCNL) is the procedure of choice for renal staghorn stones. Clinical trials those confirming the immediate effects of PCNL on renal function are limited. Although, some studies have shown that there is no correlation between PCNL and acute change in renal function [7–11] but published data in 2014 revealed that during early post-operative period following unilateral PCNL, both kidneys experienced a provisional descent in function [8]. Another publication in 2012 stated that due to damaging nature of PCNL, it could cause interference in renal task depending on its' parenchymal damage [9]. Evaluating of the changes in the glomerular filtration rate (GFR) early postoperative period showed a decrease and then an increase during the 24–48 h following tract dilatation after PCNL [10–12]. To identify acute kidney damage (AKI), there are many diagnostic biomarkers such as creatinine (Cr), kidney injury molecule-1 (KIM-1), *N*-acetyl-β-D-glucosaminidase (NAG) and liver-type fatty acid binding protein (LFABP), and NGAL [13]. Serum Cr does not command for early detection of AKI due to its' lack of ability to identify early kidney damage. NGAL is AKI biomarker which its' endogenous and molecular role in AKI remains unclear, however; it is believed to play a role in iron transportation. 1-3,7 Experimental research on animals showed that, GFR decreases immediately after PCNL and returns to baseline within the next few days [14,15]. Sharifiaghdas et al., in 2011 reported that PCNL does not cause kidney tubular injury beyond one week [16].

Although, K/DOQI (Kidney/Disease Outcomes Quality Initiative) clinical practice guidelines for chronic kidney disease recommended clearance of Cr for estimation of renal function [17], but it seems that it suffers from many disadvantages. Serum Cr concentration is dependent on age and gender and it is not able to show small changes of GFR [18]. Sometimes Cr concentration rises because of other etiologies such as when the Cr is increased due to pre-renal causes while there is no actual tubular injury [19]. Other variables may also affect the Cr concentration such as weight, muscular metabolism and drugs. Serum levels of Cr may also change with some delay after the renal injury [20]. Kardakos et al., in 2014 reported that one of the biomarker that is increasingly used as a GFR levels both in serum and urine is NGAL that is a protein mainly produced by renal tubules in response to tissue damage. Hypoxia, renal disease and malignancies can influence its values [21]. NGAL has been proved as one of the best markers for early diagnosis of AKI [22–24]. Therefore, as a guide for post-operative period management, the correlation between urine level of novel biomarker NGAL and kidney function after PCNL surgery was of interest that is investigated.

Patients and methods

Based on a cross-sectional design, 41 patients with kidney staghorn stones of larger than 2 cm, were candidate for unilateral PCNL. All patients have been informed and signed the consent form. The study was conducted to the Isfahan Kidney Transplantation Research Center and approved by the Local Ethics Committee. Patients with no evidence of obstruction such as hydronephrosis, delayed excretion or kidney damage such as size, echogenicity and scar based on radiologic evaluations were enrolled in the study from January to April 2014. The exclusion criteria were as: (1) history of renal surgery (2) renal failure (3) history of medication that potentially affect serum Cr level (4) heavy bleeding (5) those with more than one access. Demographic, clinical and surgical variables such as age, sex, size and opacity of stone, laterality, co-morbid diseases, operation time, number and site of accesses and complications during and after surgery were recorded in d-base.

Surgical technique

Under general anesthesia a 5 Fr ureteral catheter was inserted in the ureter and then secured to a Foley catheter. Patients were placed in the prone position and areas under pressure were protected with pads. Under fluoroscopic guidance, access to desired calyx was achieved using 18 gauge Chiba needle and guide wire was inserted. The tract was dilated with Amplatz dilators up to 28 Fr. Nephroscopy was performed and renal stones were fragmented with pneumatic lithoclast (SWISS lithoclast) and removed. At the end of the procedure, a 16 Fr nephrostomy tube was placed in renal pelvis.

Laboratory measurements

4 mL urine were obtained from patients 2 h before and 12 h after the procedure and sent to laboratory for measurements of NGAL levels

Table 1 Demographic data, stone characteristic and pcnl properties.

Sex	Male: 29	Female: 12	
Age	<25 y: 4	25–55 y: 23	>55 y: 14
Involved kidney	Right: 22	Left: 19	
Degree of hydronephrosis	Mild: 31	Moderate: 10	Severe:0
Opacity of stone	Lucent: 19	Opaque: 20	Semiopaque: 2
Duration of the surgery	1–1:30 h	1:30–2 h	
Punctured calyx	Lower: 35	Middle: 5	Upper: 2

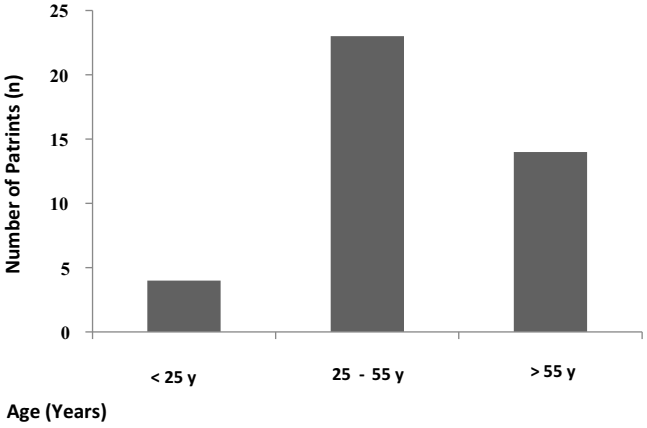

Figure 1 The distribution of age within population studied (n = 41).

that was based on ELISA Assay by the kit produced via BioVendor Company (Asheville, United States). The serum Cr levels were also evaluated through blood samples at 12 h before and 48 h after the procedure and the GFRs were calculated using the Cockroft–Gault equation.

Statistical analyses

Data were recorded in Excel and statistical analysis was performed using SPSS (SPSS Inc., Chicago, IL) for windows. Descriptive values reported as Mean ± SD. To compare groups, T-paired statistical test was used. A p value of less than 0.05 was considered as statistically significant.

Results

Table 1 shows demographic data in addition to stone characteristic and PCNL properties. Out of total population studied (n = 41), 71% were males. Fig. 1 shows the distribution of age with a minimum of 10 and a maximum of 76 years old. In the 56% of studied population the patients' age was ranged from 25 to 55 years old. However there was no significant difference related to the location of stone in right or left sides but in the 53% of the patients left kidneys were affected. There was evidence related to moderate (n = 31) and mild hydronephrosis (n = 10). Opacity of stones was as follows: Lucent in 19, opaque in 20 and semiopaque in 2. Duration of surgery was between one to two hours, with a 0.5 h longer period in females. Punctured calyx was in the 35 lower, in the 5 middle and in the 2 upper.

Table 2 shows the mean values of urinary NGAL, serum Cr and GFR levels before and after the surgery. There was a significant change

Table 2 Mean values of urinary NGAL, serum Cr and GFR levels before and after the surgery.

	Before surgery	SD	After surgery	SD	P value
Cr	1.06	0.23	1.12	0.22	0.01
NGAL	20.63	40.83	56.28	53.5	0.02
GFR	81.93	27.39	77.46	23.16	0.001

Table 3 Percentage and the number of pateints categorozed based on NGAL levels.

		Percentage	Number of patients
NGAL1	<25	89.5	34
	25–50	7.9	3
	50–75	–	–
	75–100	2.6	1
	>100	–	–
NGAL2	<25	36.8	14
	25–50	28.9	11
	50–75	15.8	6
	75–100	5.3	2
	>100	13.2	5

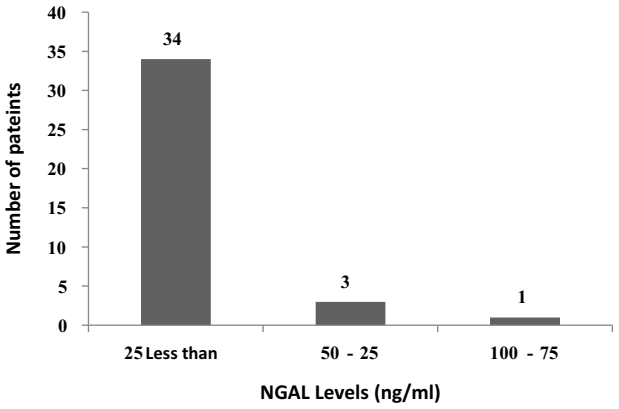

Figure 2 The distribution of NGAL (ng/mL) before surgery.

(p < 0.01) in serum Cr before and after PCNL surgery with values of 1.06 ± 0.23 (mg/dL) *versus* 1.12 ± 0.22 (mg/dL), respectively.

The mean GFR with a value of 81.93 ± 27.39 umol/L was changed significantly ($p < 0.02$) to 77.46 ± 23.16 umol/L before and after PCNL surgery (procedure) correspondingly.

Table 3 shows the percentage of patients classified based on NGAL levels (ng/mL). The mean (±SD) urine level of NGAL was significantly ($p < 0.02$) increased from 20.63 ± 40.83 ng/mL two hours before the PCNL surgery (Fig. 2) to 56.28 ± 53.5 ng/mL in twelve hours after the PCNL procedure (Fig. 3). The mean urine level of NGAL was <25 ng/mL in 89.5%, 25–50 ng/mL in 7.9% and 75–100 ng/mL in 2.6% of population studied before the PCNL surgery. These values were changed to <25 ng/mL in 36.8%, 25–50 in 28.9%, 50–75 in 15.8%, 75–100 in 5.3% and >100 in 13.2% after the PCNL surgery.

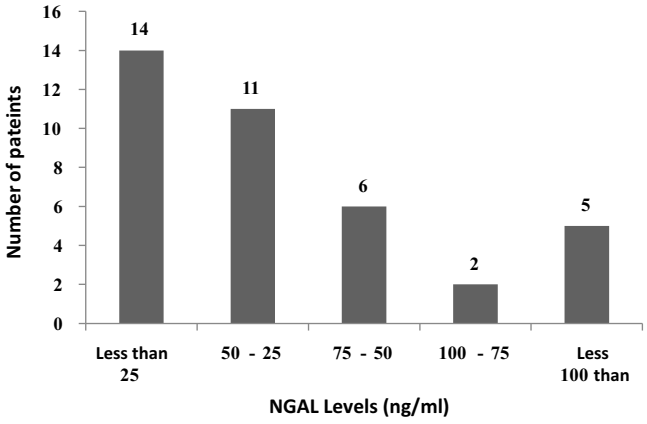

Figure 3 The distribution of NGAL (ng/mL) after surgery.

Discussion

Due to constant fluid irrigation and density, PCNL surgery may affect renal function.There are several studies that evaluated the long term kidney injuries but not AKI after PCNL surgery. Previous publication reported that once AKI develops, mortality remains to be high [25,26]. Injured kidney tubular cells create and discharge numerous biological elements related to distinctive and developed inflammatory immune responses, including NGAL. The biological character of NGAL in this location may be to decline damage by plummeting apoptosis and increasing the regular proliferation of kidney tubule cells. Because of its capability to perform as a growth factor, NGAL has also been establishing to have a renoprotective consequence in acute ischemic renal injury in an animal model [26].

In the present study performed on 41 patients with a mean age of 47 (ranged; 20–70 years old), those suffered from kidney staghorn stones after PCNL surgery, there were a significant increase and decrease in mean serum Cr and GFR respectively. Related to Cr, in agreement with previous publications in the absences of significant reduction in GFR, to diagnose renal tubular injury, it cannot be considered for the evaluation of AKI, because of its' insensitivity and unreliability [4–28]. Related to GFR, Nouralizadeh et al., in 2011 studied renal effects of PCNL immediately after surgery. They also reported that renal GFR reduced instantly after PCNL extended to baseline 48 h after operation and then increased slowly [12].

In this study there was a significant increase ($p < 0.02$) in the mean value of NGAL from 20.63 ng/mL two hours before to 56.28 ng/mL twelve hours after the PCNL procedure.

Mishra et al. showed that the urine levels of NGAL, 2 h after the cardiopulmonary bypass could predict AKI with an AUC of 0.998.6. Other studies also showed that the urine level of NGAL, 6 h after heart surgery could predict AKI with an AUC of 0.775 [22–24].

However, in 2011 Sharifiaghdas et al., mentioned that PCNL does not cause kidney tubular injury beyond one week,but in patients with pre-operative elevated Cr, diabetes mellitus, the incidence of AKI is higher than the others [16]. Tabibia et al., in 2014 confirmed that avoidance of significant perioperative bleeding is an important point to prevent post PCNL renal insufficiency [26]. In a recent publication (2015) by Zhao et al., there is concern that after the joined management of percutaneous nephrostolithotomy with flexible ureteroscopy, the concentrations of NGAL, Cys-C and KIM-1 are expressively augmented, proposing damages on renal function [27]. In another publication by Daggülli et al., in 2015 confirmed a significant difference between the mean preop and postoperative (postop) 24 h NAG/Cr values ($p < 0.001$). Also, postop 24 h NGAL/Cr levels were statistically significant, higher than its preoperative levels ($p = 0.013$) [28]. Finally like any other invasive method in surgery, considering the trauma to renal tissue, the PCNL procedure also has its' own general and specific complications. The fluctuation in the level of NGAL, GFR and Cr and its' correlation with AKI, duration of hospital stay, co-morbidity and related complications need further justification due to the small sample size and the lack of NGAL measurements after a longer period of time.

Conclusions

To understand the extent of AKI after the PCNL procedure in Iranian population with kidney staghorn stones, NGALcould be used as a reliable biomarker. However further research related to its' correlations with the: (1) extent of AKI (2) higher stone-free rates (3) shorter hospital stays and (4) decrease in morbidity rates seem to be advantageous.

Authors' contributions

Associate Professor Mehrdad MohamadiSichani contributed to the study concept, literature review, acquisition of data, design, analysis and interpretation of manuscript, drafting of the manuscript and critical revision of the manuscript for intellectual content.

Assistant Professor Zahra Tolou_Ghamari contributed to the literature review, acquisition of data and interpretation of manuscript, drafting of the manuscript and critical revision of the manuscript for intellectual content.

Ethical committee approval

The Ethics Committee of Isfahan Kidney Transplantation Research Center approved this study.

Disclosure

The study was supported by Isfahan University of Medical Sciences.

Conflict of interest

The authors declare that there is no any conflict of interest regarding to this study.

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