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Neutrophil Gelatinase-Associated Lipocalin Levels During Pneumoperitoneum

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ABSTRACT

Background and Objectives: A temporary deterioration in renal function during pneumoperitoneum has been reported, but the extent is not known. A new marker for the early detection of renal injury, neutrophil gelatinase-associated lipocalin (NGAL), has been shown to increase in various conditions that affect renal function. This study was conducted to explore detrimental effects of pneumoperitoneum in laparoscopic surgery on renal function by studying levels of urinary NGAL (uNGAL).

Methods: Thirty-two women scheduled to undergo laparoscopic surgery in a gynecology clinic were recruited. NGAL was measured in urine collected at the beginning (0 h) and at 2 and 24 hours after the initiation of surgery. Hemodynamic parameters were analyzed immediately after intubation and before desufflation.

Results: Levels of uNGAL increased from 5.45 ng/mL at 0 hours to 6.35 ng/mL at 2 hours and to 6.05 ng/mL at 24 h; however, there was no significant change in uNGAL levels at the collection time points. Intraoperative oliguria was observed in all cases, and the severity increased with the duration of surgery. uNGAL levels did not correlate with the duration of surgery or pneumoperitoneum.

Conclusion: In patients with normal renal functions, pneumoperitoneum results in transient oliguria without any early renal damage, as indicated by nonsignificant changes in uNGAL levels.

Key Words: Laparoscopy, Neutrophil Gelatinase-Associated Lipocalin, pneumoperitoneum, renal function.

INTRODUCTION

Laparoscopic surgery is a widely employed method used in gynecologic surgeries, often with prolonged periods of pneumoperitoneum. Generally, establishment of pneumoperitoneum during laparoscopy can result in respiratory, cardiovascular, and urinary system changes. The insufflation of carbon dioxide (CO_2) and the rise of the intra-abdominal pressure induced by pneumoperitoneum have hemodynamic effects that may also alter renal perfusion and function.[1] Although an intra-abdominal pressure of up to 14 mm Hg has no clinically relevant effects in healthy subjects (American Society of Anesthesiology Class I and II), there is sufficient evidence to indicate that renal function temporarily deteriorates during pneumoperitoneum.[2]

Pneumoperitoneum-related renal effects are difficult to determine and monitor. In most studies, urine output and creatinine clearance have been used as indicators of altered renal function but they are neither useful nor ideal markers of renal function in an acute setting.[2] Molecular markers for the early detection of renal injury would enable more accurate results that would clarify the effects of pneumoperitoneum on renal functions. These markers include neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule (KIM)-1, interleukin (IL)-18, and liver fatty acid-binding protein (L-FABP). NGAL is a small 25-kDa protein expressed on tubular cells and belongs to the well-defined lipocalin superfamily of proteins. It is a rapid biomarker of kidney injury and recovery that exhibits a significant change during the clinical course of various renal disorders.[3] For example, levels of NGAL significantly increase, as early as 2 to 4 hours after renal injury, before rising serum creatinine levels can be detected,[4,5] in response to tubular stress such as ischemia or toxicity.[6–8]

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There have been few studies evaluating NGAL levels during pneumoperitoneum, and contradictory results have been reported.[1,9] As NGAL may be a marker that contributes to the understanding of the magnitude of decrease in renal function during pneumoperitoneum, the goal of this study was to explore any detrimental effects of the duration of pneumoperitoneum on renal functions by quantifying urinary (u)NGAL levels in patients undergoing laparoscopic surgery with standard anesthesia and physical positioning in patients with normal preoperative renal function.

MATERIALS AND METHODS

This study was approved by the Institutional Ethics Committee (Approval: 180620143). Written informed consent was obtained from all study participants. Women of reproductive age, who were scheduled for laparoscopic surgery for various benign gynecologic conditions, were recruited into the study from July 2014 through April 2015. Exclusion criteria for this study were pregnancy, urinary tract infection, acute or chronic renal failure, cardiovascular disease, hypoxic–ischemic vascular disease, conversion to laparotomy, and hemodynamic instability. Intraoperative heavy bleeding is defined as patients that required blood transfusions, and these cases were excluded from the study. To limit hemodilution, hematocrit >21% and hemoglobin >7 g/dL was maintained during surgery. Nephrotoxic medications (nonsteroid anti-inflammatory drugs, aminoglycoside antibiotics, β-lactams, sulfonamides, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers) were not used in any of the cases. Suspicion of venous gas embolism (sudden arterial hypoxemia, hypercapnia, decreased end tidal [ET]co_2, and arrhythmias) was another exclusion criterion. Finally, those who were unwilling to participate were also excluded.

All patients received general anesthesia with the combination of 2.5 mg/kg propofol, 1 μg/kg fentanyl, and 0.6 mg/kg rocuronium. General anesthesia was maintained with the combination of 1.5–2.5% sevoflurane, 2 L/min oxygen, 2 L/min nitrous oxide, and 0.15 mg/kg rocuronium (at 30-minute intervals and as needed). All patients received pressure-controlled ventilation, volume guaranteed (PCV-VG) without positive end expiratory pressure (PEEP). The respiratory rate was adjusted to achieve normocarbia. After anesthesia induction, a 20-gauge radial arterial catheter was inserted to obtain hemodynamic measurements and collect blood samples. Urethral catheterization was performed to collect urine samples. Pneumoperitoneum was established by insufflation of carbon dioxide gas through automatic insufflators. A maximum 15 mm Hg intra-abdominal pressure was maintained throughout the operation. For the surgery, the patient was placed in the Trendelenburg position at a 30° angle, measured by a protractor. Intraoperative fluid management was performed by estimating fluid requirements at 10 mL/kg of ideal body weight and adjusted according to intraoperative mean arterial pressure (MAP). The intraoperative MAP was held between 65 and 75 mm Hg. Balanced crystalloids (eg, Ringer's lactate or Isolyte; B Braun Medical, Bethlehem, Pennsylvania, USA), instead of colloids, were preferentially used. The duration of surgery was defined as the period between intubation and extubation. The duration of pneumoperitoneum was defined as the time between insufflation and desufflation.

Hemodynamic parameters such as heart rate (HR), MAP, $ETco_2$, and expiratory tidal volume (VTexp) were obtained at 10-minute intervals after anesthesia was induced. Intraoperative pH, base excess (BE), HCO_3, $Paco_2$, arterial to $ETco_2$ pressure gradient (Pa-$ETco_2$), and dynamic pulmonary compliance (Cdyn) were measured immediately after intubation and immediately before desufflation to document the effects of pneumoperitoneum.

Preoperative renal function was evaluated by determining blood urinary nitrogen (BUN), creatinine, and cystatin C levels. Serum creatinine was measured by the kinetic alkaline picrate methodology, and BUN was measured by enzymatic calorimetric assay by commercially available kits (Abbott Architect *c*Systems Assay Parameters-Clinical Chemistry; Abbott Diagnostics, Lake Forest, Illinois, USA). Cystatin C was measured by immunoturbidimetric quantitative measurement with a commercially available kit (Abbott Architect Systems Assay Parameters, Sentinel CH, Milan, Italy). eGFR was calculated by 2009 chronic kidney disease, epidemiologic collaboration (CKD-EPI) creatinine equation.[10] After induction of anesthesia urethral catheterization was performed to collect the first urine sample (0 hours). Urine and blood samples were collected immediately after catheterization (0 h) and at 2 and 24 hours after the initiation of surgery. In addition, the intraoperative and 24-hour postoperative urine outputs were recorded.

The collected urine samples were stored at −80°C until analysis. uNGAL levels were measured by the chemiluminescence microparticle immune assay (CMIA) using the Abbot Architect *i*1000 immunology analyzer with a commercially available kit (Abbott Ireland Diagnostic Divi-

sion, Sligo, Ireland). The intra-assay and interassay coefficients of uNGAL were 2.2 and 1.4%, respectively.

Statistical Analysis

Statistical analyses were conducted with SPSS for Windows, ver. 22.0 (SPSS Inc., Chicago, Illinois, USA). The Kolmogorov-Smirnov test was used to determine whether the distribution of continuous variables was normal. The Levene test was used to evaluate the homogeneity of variance. To compare 2 independent groups, the Student's *t* test was used for normally distributed variables, and the Mann-Whitney U test was used for abnormally distributed data. To compare paired groups, the Student's *t* test was again used for normally distributed variables, and the Wilcoxon signed rank test was used for abnormally distributed data. For more than 2 dependent groups, the repeated-measures *t*-test was used to analyze differences in normally distributed variables. Pearson and Spearman correlation analyses were performed to evaluate the degrees of relation between variables. $P < 0.05$ was considered significant.

RESULTS

During the study period, 60 patients fulfilled the inclusion criteria and 51 agreed to participate. After the study began, 19 patients withdrew or were asked to withdraw from the study for various reasons, including early discharge (n = 9), blood/urine sample loss (n = 7), and heavy bleeding/transfusion (n = 3). Demographic data and renal function tests were collected for the 32 patients, and statistical analysis was performed (**Table 1**). The laparoscopy was performed for diagnostic purposes in 9 patients (28.1%), tubal ligation in 6 patients (18.8%), for ectopic pregnancy in 4 patients (12.5%), laparoscopic-assisted vaginal hysterectomy in 3 patients (9.4%), ovarian drilling in 3 patients (9.4%), endometriosis treatment in 3 patients (9.4%), adnexal mass treatment in 3 patients (9.4%), and myomectomy in 3 patients (9.4%).

Table 1.
Demographic Data and Preoperative Renal Function Tests of the Patients

	Mean (SD)	Median (Min-Max)
Age (years)	33.7 (8.3)	34.5 (18–54)
Height (cm)	164 (4.8)	165 (150–170)
Weight (kg)	68.1 (9.5)	67 (54–90)
BMI (kg/m^2)	25.3 (3.8)	24.6 (19.1–37.5)
BUN (mg/dL)	9.75 (1.83)	9.00 (7.0–15.0)
Creatinine (mg/dL)	0.66 (0.08)	0.65 (0.46–0.89)
Cystatine (mg/L)	0.51 (0.18)	0.50 (0.13–0.92)
eGFR (CKD-EPI 2009)	114.53 (11.10)	114.00 (84.0–138.0)

n = 32.

BUN levels significantly decreased at 24 hours when compared to 0 hours. However, the changes in serum creatinine and uNGAL levels at 2 and 24 hours were not statistically significant compared to 0-hour (baseline) values ($P > .05$; **Figure 1**). The median (min–max) level of uNGAL at 0 hours was 5.45 ng/mL (range, 0.01–89.80 ng/mL). The level increased to 6.35 ng/mL (range, 0.01–47.50 ng/mL) 2 hours and decreased to 6.05 ng/mL (range, 0.10–28.00 ng/mL) at 24 hours. The uNGAL levels at 2 and 24 hours correlated positively with baseline levels (r = 0.561, $P = .001$ at 2 hours; r = 0.421, $P = .016$ at 24 hours). Notably, intraoperative oliguria was observed in all cases (27.46 ± 18.49 mL/h) and urine output returned to normal at 24 hours in all cases (93.67 ± 27.85 mL/h). In cases where the surgery was longer than 60 minutes, the decrease in urine output was more significant (**Table 2**).

The mean duration of the pneumoperitoneum and the surgery were 52.8 ± 39.1 and 76.7 ± 40.3 minutes, respectively. For further analysis, the patients were grouped according to the duration of surgery (>60 min [n = 16] vs ≤60 minutes [n = 16]). Baseline and 2- and 24-hour uNGAL levels were similar in each group (**Table 2**). The correlation analysis performed to evaluate the association between uNGAL levels at different time points and the duration of surgery or pneumoperitoneum was nonsignificant (r = −0.118, $P = .522$; r = 0.0.74, $P = .688$). The hemodynamic and ventilatory variables measured immediately after intubation and immediately after desufflation are given in **Table 3**. Only, the intraoperative changes in HCO_3 levels correlated negatively with uNGAL levels (r = −0.596, $P = .012$).

DISCUSSION

In the current study, we sought to elucidate the physiological effects of pneumoperitoneum on renal functions. CO_2 pneumoperitoneum in laparoscopic surgery for benign gynecological conditions resulted in transient oliguria without any early renal damage, as assessed using uNGAL protein quantification. Even in patients with normal preoperative renal function, prolonged periods (>1 h) of pneumoperitoneum were associated with a larger decrease in urinary output. Increased intra-abdominal pressure leads to decreased perfusion of the intra-abdom-

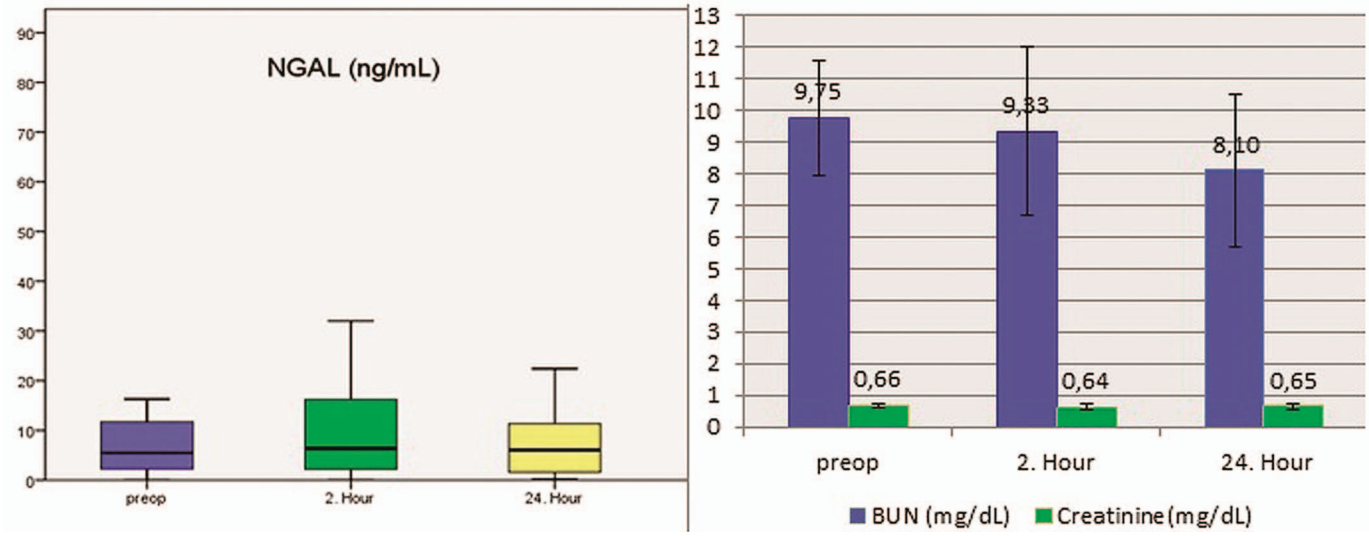

Figure 1. Preoperative (0 hours) and postoperative 2 and 24 hours uNGAL, BUN, and creatinine levels.

Table 2.
uNGAL Levels and Urine Output Data in Groups Defined by Duration of Surgical Procedure

	Duration of Surgical Procedure (min)		
	≤60	>60	
	(n = 16)	(n = 16)	*P*
Preop uNGAL (ng/mL)	5.20 (0.01–89.80)	5.75 (0.01–89.70)	.678
Postop 2 h uNGAL (ng/mL)	5.50 (0.01–40.20)	7.05 (0.01–47.50)	.880
Postop 24 h uNGAL (ng/mL)	6.70 (0.20–28.00)	6.22 (6.05–20.00)	.763
Intraop urine output (mL)	35.15 ± 20.74	20.25 ± 2.94	.022*
Postop urine output (mL)	92.64 ± 25.76	94.64 ± 30.50	.846

uNGAL data are the median (range). Output data are the mean ± SD.
*$P < 0.05$.

inal organs that play a major role in the change in pH values, as observed in this study.

In major operations, hypovolemia, low systemic vascular resistance, and direct injury to the renal system are common events that can harm the kidney.[11] There are no unique data about gynecologic cases, but the incidence of acute kidney injury (AKI) has been reported as ~1% for general surgery or as high as 25–30% after cardiac surgery.[12] The risk of renal injury mainly depends on previously determined risk factors. In a study with a large number of cases (76,000 general surgical patients), the General Surgery AKI Risk Index was developed based on separate preoperative risk factors listed as age 56 years or older, male sex, emergency surgery, intraperitoneal surgery, diabetes mellitus necessitating oral therapy, diabetes mellitus necessitating insulin therapy, active congestive heart failure, ascites, hypertension, mild preoperative renal insufficiency, and moderate preoperative renal insufficiency.[13] In patients like ours, having 0 to 2 risk factors, the incidence of AKI is 0.2%.[13] In our study, the limited number of cases hindered our drawing strong conclusions because of the low incidence of AKI in a healthy population without risk factors. Regarding postoperative AKI, an episode of hemodynamic instability in the perioperative period is the most common predisposing factor. Therefore, maintenance of normal renal perfusion during and after surgery is perhaps the most important prophylactic measure.[14] In a meta-analysis AKI is significantly

Table 3.
Hemodynamic and Respiratory Variables Immediately After Intubation (T0) and Immediately Before Desufflation (T1)

Variable	T0	T1	*P*
Intraop HR	79.47 ± 12.12	70.41 ± 8.24	.001**
MAP	97.06 ± 15.17	91.47 ± 11.72	.122
İntraop BE	4.67 ± 3.22	6.07 ± 3.12	.001**
İntraop HCO_3	20.72 ± 2.91	19.42 ± 2.62	.001**
İntraop pH	7.39 ± 0.06	7.34 ± 0.06	.006*
İntraop $Paco_2$	30.74 ± 4.59	33.23 ± 4.66	.105
Vtexp	459.53 ± 35.96	463.94 ± 28.35	.691
$ETco_2$	33 (29–37)	32 (19–45)	.861
Pa-$ETco_2$	0 (0–12.70)	0 (0–13.2)	.114
Cdyn	24.91 ± 6.38	21.84 ± 3.82	.049*

Data are the mean ± SD, with the exception of the $ETco_2$ data, which are the median (range).
*$P < 0.05$; **$P < 0.01$.

reduced by perioperative hemodynamic optimization in the pre-, intra- or postoperative period.[15] Thus, in our study, to optimize renal outcomes, fluid management was controlled and adjusted according to intraoperative MAP.

In a systematic review, 17 of 20 studies demonstrated that decreased renal blood flow after pneumoperitoneum was dependent on the magnitude of intra-abdominal pressure.[2] The suitable CO_2 pneumoperitoneal pressure for renal microcirculation is <8 mm Hg for laparoscopic surgery.[16] Even if pneumoperitoneum can alter renal perfusion, it seems to be clinically safe up to 15 mm Hg.[17] In our study, although a direct measurement of renal blood flow was not available, the decreased urine output indicates possibly diminished renal perfusion, despite no change in MAP during the operation. Therefore, the perioperative oliguria observed in this study may have been a physiological result of increased intra-abdominal pressure, supporting previous reports.[18]

It has also been reported that, during pneumoperitoneum, oliguria may be caused by increased abdominal pressure and local compression of renal vasculature associated with increased plasma renin activity.[19,20] In addition, CO_2 indirectly absorbed from the peritoneum increases systemic vascular resistance, leading to the activation of renin/angiotensin/aldosterone (RAA). This effect may also be a contributing factor to the observed oliguria. However, renin and RAA were not measured in our study. Thus, we are not able to determine whether renin or RAA or both were responsible for the oliguria.

During laparoscopy, the absorption of CO_2 by the peritoneum is associated with a risk of hypercapnia and can lead to respiratory acidosis.[1] We did not detect any statistically significant changes in $Paco_2$ related to pneumoperitoneum. The ventilatory settings were adjusted according to ETco, to achieve normocarbia throughout the procedure. As the measured values of respiratory products did not change significantly, the significant drop in pH values may have occurred because of reduction of intra-abdominal organ perfusion. As a result, in our study, decreased renal cortical perfusion during laparoscopy[21] may have caused a statistically significant reduction in HCO_3 levels, indicating subclinical and transient tubular dysfunction. Notably, the negative correlation between uNGAL and HCO_3 levels also indicates tubular stress. The HCO_3 reabsorption occurs predominantly in the proximal tubule, similar to NGAL, which is also filtered and reabsorbed by the normal proximal tubule.[22] Finally, the decrease in BE values along with decreased pH and HCO_3 values is suggestive of alkaline reserve (BE) consumption to compensate for the ischemia of intra-abdominal organs, as previously reported by Hypolito et al.[23]

Previous studies, primarily of animal model systems, report that prolonged pneumoperitoneum affects renal blood flow and causes a reduction in urine output and creatinine clearance.[21,24,25] This effect is a transient one, lasting 2 hours before normal conditions were restored.[21] Histological examination suggested that shorter pneumoperitoneum periods (up to 5 hours) had no observable effect compared with control groups in rat models,[26,27] whereas a porcine model subjected to significantly longer pneumoperitoneum (24 hours) exhibited low-grade proximal renal tubule damage.[28] This result led to the conclusion that extremely long periods of pneumoperitoneum predispose functional and morphologic kidney impairment.[28] To our knowledge, only one of these studies of a rat model system has used NGAL to evaluate renal functions during pneumoperitoneum. No difference was reported in the renal expression of NGAL after 1 and 2 hours of pneumoperitoneum.[29] In support of this result, we also did not detect a significant difference in uNGAL levels when surgery was longer than 60 min. NGAL is an accurate method for facilitating the early detection of kidney damage.[30] Moreover, NGAL has a good predictive value with reference to mortality rates (OR 8.8, 95% CI 1.9–40.8; area under the curve [AUC]–receiver operating characteristic [ROC] 0.706) and renal replacement requirements during hospitalization (OR 12.9, 95% CI 4.9–33.9; AUC-

ROC 0.782).[30] Consequently, further large population studies of NGAL, an early biomarker of renal function, for longer periods of pneumoperitoneum is needed to clarify the potential benefit of this marker for mortality rates and renal replacement requirements.

In conclusion, short periods of pneumoperitoneum do not induce notable renal damage, although it can alter renal function. As the routinely used laboratory markers, such as urea and creatinine, are not sufficiently sensitive for early detection of subclinical acute kidney injury, NGAL levels that enable the diagnosis of renal damage within 2 hours of the injurious event show great promise. In the future, commercially available NGAL assays may provide assessment of complementary aspects of renal injury during CO_2 pneumoperitoneum, and immediate results can help optimum perioperative hemodynamic management and measures.

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