



Impact of Pneumoperitoneum on the Post-Operative Renal Function and Level of Acute Kidney Injury Markers: Comparison between Laparoscopic and Open Nephrectomy

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Abstract

Purpose: As laparoscopic surgery becomes more widespread, understanding the adverse effects of pneumoperitoneum becomes more important, especially in patients subjected to laparoscopic unilateral nephrectomy. The purpose of the current study was to investigate the effect of pneumoperitoneum on the remnant kidney after laparoscopic nephrectomy compared to open surgery.

Methods: The study group included 30 patients. 22 patients underwent laparoscopic nephrectomy whereas 8 patients underwent open nephrectomy. Serum and urine samples were collected before surgery, 8 and 24 hours after surgery. At these time points' urine levels of NGAL and KIM-1, two novel biomarkers for acute kidney injury (AKI) were also determined.

Results: Following surgery serum creatinine slightly increased in both groups but then decreased in those who had open procedure compared with the laparoscopic cases where it continued to increase. Urinary NGAL, but not urinary KIM-1, increased in both groups after 8 and 24 hours. The pattern of change of both urinary markers (NAGL and kim-1) after surgery was not affected by the use of pneumoperitoneum compared to the open procedure. More patients in the laparoscopic group developed acute kidney injury (41% vs. 12%).

Conclusions: The present study shows a negative effect of pneumoperitoneum on the kidney function in patients undergoing laparoscopic nephrectomy compared to the open procedure. NGAL and KIM-1 urinary levels were not affected by the increased intra-abdominal pressure.

Keywords: KIM-1; Nephrectomy; NGAL; Pneumoperitoneum; Renal function

Introduction

Minimally invasive surgery continues to gain popularity and widespread acceptance due to its clear advantages. During laparoscopic surgery, pneumoperitoneum is mandatory to allow adequate exposure. It is, however, may be associated with oliguria, decreased glomerular filtration rate (GFR) and renal perfusion [1-2]. The exact mechanism of renal dysfunction secondary to pneumoperitoneum is not fully understood. This may be related to direct compression of the renal parenchyma and vasculature that leads to reduced renal blood flow [3]. The consequence is an increased stimulation of the renin-angiotensin-aldosterone system (RAAS) and exertion of antidiuretic hormone [4]. The result is salt and water retention leading to oliguria.

We have previously reported the association between pneumoperitoneum and kidney injury in rat model [5]. Others reported similar results in human [6,7]. These results may be of clinical significance especially in patients remaining with a single kidney after laparoscopic nephrectomy. Unfortunately, there is very small number of human studies in the literature addressing this important topic. One study investigated the effect of pneumoperitoneum after laparoscopic donor nephrectomy [8]. However, donor patients were healthy and rigorously screened for preexisting comorbidities and the patients were not compared to open procedure.

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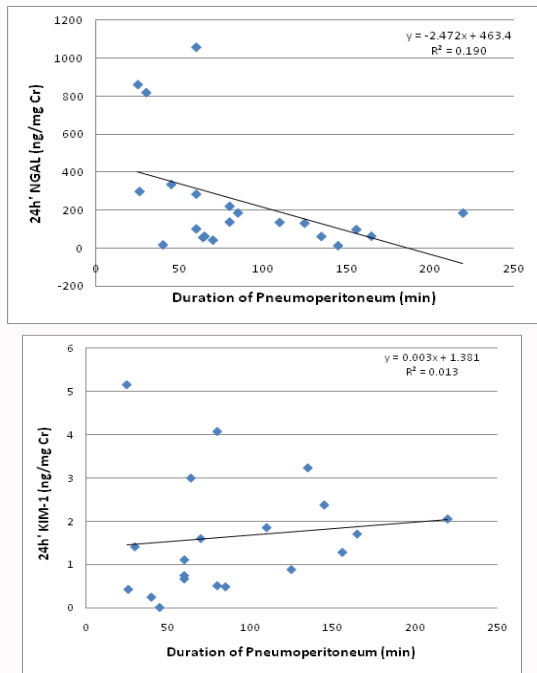


Figure 1A and B: Correlation between the duration of pneumoperitoneum and the post-operative urinary levels NGAL and KIM-1.

The aim of the current study was to quantitatively document in patients after unilateral nephrectomy the possible deleterious effect of pneumoperitoneum on the residual kidney function by serial measurements of serum creatinine and the urinary level of two novel biomarker for early kidney injury, namely neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule- 1 (KIM-1). The results were compared between two groups of patients who underwent laparoscopic and open procedures.

Material and Methods

Patients

This is a non randomized prospective study that was carried out after achieving the IRB approval and an informed consent was obtained from all individual participants included in the study. The study group included 30 patients who underwent nephrectomy for various causes. 22 patients underwent laparoscopic surgery and 8 open approaches. Patients with active chronic infection were excluded from the study.

Pre and post-operative renal function of the studied patients was assessed either by serum creatinine level or by estimated glomerular filtration rate (eGFR) using the MDRD equation. AKI was considered either when SCr level increased by more than 50% or by 0.3 mg/dL from baseline [9,10].

All patients have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Surgical technique

Open technique: All open nephrectomies (ON) were performed through a subcostal incision approximately 2.0 cm below the costal margin. The rectus abdominis muscle was divided as were the ipsilateral external and internal obliques and the transversus

abdominis muscles. The peritoneum was entered and an Omni retractor was positioned to expose the operative field. The white line of Toldt was incised and the colon reflected medially to expose the renal vessels. The kidney was then bluntly mobilized posteriorly and laterally in the avascular plane between Gerota's fascia and quadratus lumborum and psoas muscles. At the inferior portion of the kidney the ureter was identified ligated and divided. The renal artery and vein were identified, cleaned of surrounding fibrofatty tissue, doubly ligated and divided. The superior portion of the Gerota's fascia was freed and the whole surgical specimen was removed.

Laparoscopic technique: All laparoscopic procedures were performed via a transperitoneal approach in the modified lateral decubitus position. The Veress needle was used for insufflation and the 10 mm laparoscope port was inserted in the midclavicular line 2 to 3 cm at or just above the umbilicus. A 12 mm port was inserted in the anterior axillary line 2 cm below the costal margin, and a 10 mm port was placed on the anterior axillary line at the level of the anterior iliac crest. A 5 mm port was placed in the midline for liver retraction on right-sided nephrectomies. The colon was mobilized medially after incision along Toldt's line, and the gonadal vein was located and traced to the renal vein or inferior vena cava. The hilum was dissected and the artery was secured with vascular clips and the vein was stapled with the vascular endo-GIA stapler. The intact specimen was placed in an endocatch bag and removed through an extension incision at the level of the 12 mm port site. Port sites were closed with sutures and skin clips.

Samples collection

Voided urine samples were collected for all patients before surgery, 8 and 24 hours following nephrectomy. The collected urine samples were stored at -80°C until analysis.

Determination of urinary NGAL and KIM-1

NGAL and KIM-1 were determined from a single 10µl specimen of urine and were measured with commercially available ELISA kits (NGAL Rapid ELISA Kit; Bio Porto Diagnostics, Gentofte, Denmark) and (Wuhan EIAab Science Co. Wuhan, China), respectively.

Statistical analysis

Data are presented as mean±S.E.M (standard error of the mean). One-way analysis of variance (ANOVA) for repeated measures, followed by Dunnett's test, was used for comparison of values from the different post ischemia periods with baseline values. P value of $p < 0.05$ was considered statistically significant.

Results

A total of 30 patients (19 males and 11 females) who underwent unilateral laparoscopic nephrectomy (n=22) or open nephrectomy (n=8) were included in the current study. The baseline characteristics of the laparoscopic and open groups were similar in term of age, comorbidities, tumor characteristics, preoperative baseline serum creatinine and estimated GFR. With respect to urine biomarker levels, while KIM-1 urine concentration did not differ significantly between the studied groups, the urinary NGAL level was lower in the open group (Table 1).

Table 2 summarizes the pattern of post-operative changes of the studied biomarkers as well as serum creatinine. Assessment of urinary level of NGAL 8 and 24 hours after nephrectomy demonstrated gradual elevation compared with the pre-operative values in both groups.

Table 1: Clinical characteristics of patients undergoing laparoscopic and open nephrectomy.

Variable	Lap (n=22)	Open (n=8)
Mean age (year)	61.18±2.91	68.7±3.54
Gender: Male/Female	13/9	2-Jun
Side Right/Left	17-May	3-May
Tumor Location Central/Peripheral	14/8	2-Jun
Mean Tumor Size (cm)	6.21±0.44	6.97±1.31
Pre Op' Serum Creatinine (mg%)	1.08±0.073	1.012±0.09
NGAL/Ucr (Pre Op') (ng/mg Cr)	192.36±51.7	85.8±27.7
KIM-1/Ucr (Pre Op')(ng/mg Cr)	2.96±0.67	2.39±0.84
Mean eGFR (pre Op')(ml/min)	87.2±5.6	83.8±8.45
Patients with comorbidities	17 HTN; 10 DM; 3 IHD; 1 Nephrolithiasis; 9 dyslipidemia	5 HTN; 5 DM; 0 IHD; 1 Nephrolithiasis; 4 dyslipidemia

Table 2: Post-operative changes of urinary NGAL and KIM-1 as well as serum creatinine in patients treated by laparoscopic and open nephrectomy.

Open	LAP	
85.8±27.6	192.3±51.7	Baseline NGAL
		(ng/mg Cr)
		8h' NGAL
268.9±98.7	210.24±71.9	(ng/mg Cr)
		24h' NGAL
		(ng/mg Cr)
354.6±231.7	246.16±64.4	Baseline KIM-1
		(ng/mg Cr)
		8h' KIM-1
2.39±0.84	2.96±0.67	(ng/mg Cr)
		24h' KIM-1
		(ng/mg Cr)
1.73±0.87	1.88±0.3	Baseline Creatinine
		mg%
		8h' Creatinine
1.12±0.54'	1.64±0.3	mg%
		24h' Creatinine
		(P=0.0184)
1.012±0.09	1.08±0.073	mg%
		8h' Creatinine
		mg%
1.325±0.186	1.45±0.118*	24h' Creatinine
		mg%
		(P=0.01)
1.18±0.14		mg%

When urinary level of KIM-1 was studied at the same time points before and after surgery a different pattern was observed, i.e. the urinary concentration of the marker gradually decreased regardless of the operative method used. The patterns of change of the studied markers were not affected by the pneumoperitoneum.

Evaluation of post nephrectomy serum creatinine demonstrated early (8 hours) similar increase in both groups of 0.23 mg% and 0.31 mg% for laparoscopic and open groups respectively (p=0.83). Further measurements revealed continuous elevation of the creatinine in the patients managed by laparoscopy (up to 1.45 mg %) but decreased level in the open surgery cases (up to 1.18 mg %). Such pneumoperitoneum related decrease in the laparoscopic group is statistically significant (P=0.01).

Additionally, we examined the impact of pneumoperitoneum duration in patients treated by laparoscopic procedures on the urinary levels of NGAL and KIM-1. As presented in Figure 1A and 1B, there was no correlation between the duration of pneumoperitoneum and

the post-operative urinary levels of the studied markers.

During the postoperative period, 10 patients (33%) developed acute kidney injury (AKI). Only one (12%) among the open surgery group compared with nine cases (40%) in patients subjected to pneumoperitoneum. (Table 3) presents the baseline and post operative urinary levels of NGAL and KIM-1 normalized to urine creatinine among patients with and without AKI in the laparoscopic group. As shown these biomarkers did not demonstrate a different pattern in terms of urinary concentration changes among the two sub-groups (AKI vs. Non-AKI). We further looked at clinical variables and their association with peri-operative functional outcome that define the two categories. As demonstrated in Table 4 the basal renal function was statistically significantly lower in patients who developed AKI, i.e. before surgery eGFR of 50.43 vs. 82.70 (P<0.0001) and serum creatinine 1.205 vs. 1.005 (P=0.0004) for AKI and Non-AKI patients respectively. Patients in the AKI group were on average 10 year older, had slightly smaller lesions (mean size 5.65 cm vs. 6.63 cm) and their surgical procedure was associated with reduced blood loss. By contrast no difference in rate of relevant comorbidities or duration of pneumoperitoneum was observed between the two sub-groups.

Discussion

The expansion of minimally invasive laparoscopic surgery emphasizes the essential need to understand the adverse effects of pneumoperitoneum which is an essential part of this therapeutic modality. This is particularly important in cases of laparoscopic nephrectomy, because maintaining the function of the remnant kidney is critical. Increased intra-abdominal pressure associated with pneumoperitoneum leads to compression of the kidney parenchyma, reduced cardiac output and systemic hormonal effects, which result in decreased glomerular filtration rate (GFR) and urinary output [1-5]. In a review of five animal studies, Shafer et al. demonstrated a decrease in renal perfusion ranged from 12% to 14% [11]. Miki et al. [12] reported a decreased urine output and GFR in patients after laparoscopic cholecystectomy, whereas no significant changes in these parameters were observed when an abdominal lift device was used.

The present study shows a negative effect of pneumoperitoneum on the post-operative kidney function in patients undergoing laparoscopic nephrectomy. This is evident by the further decrease of serum creatinine (beyond 8 hours) after surgery which was not observed in the open nephrectomy group. Moreover, the rate of AKI after laparoscopic surgery was 3.4-fold higher compared with those

Table 3: Relationship between urinary NGAL and KIM-1 levels in patients with and without AKI in patients treated by laparoscopic nephrectomy.

Post operation				Baseline		Parameter
24 Hours		8 Hours		AKI-Patients	Non-AKI patients	
AKI-Patients	Non-AKI patients	AKI-Patients	Non-AKI patients			AKI-Patients
R ² =0.47	R ² =0.13	R ² =0.47	R ² =0.06	R ² =0.46	R ² =0.0009	Urinary NGAL (ng/mg Cr)
Pvalue=0.06	Pvalue=0.09	Pvalue=0.059	Pvalue=0.28	Pvalue=0.06	Pvalue=0.89	
R ² =0.07	R ² =0.106	R ² =0.12	R ² =0.018			% change of Urinary NGAL
Pvalue=0.49	Pvalue=0.149	Pvalue=0.39	Pvalue=0.55			
R ² =0.0007	R ² =0.06	R ² =0.018	R ² =0.03	R ² =0.06	R ² =0.002	Absolute KIM-1 (ng/mg Cr)
Pvalue=0.94	Pvalue=0.29	Pvalue=0.75	Pvalue=0.45	Pvalue=0.53	Pvalue=0.82	
R ² =0.04	R ² =0.0006	R ² =0.001	R ² =0.018			%change of Urinary KIM-1
Pvalue=0.63	Pvalue=0.915	Pvalue=0.93	Pvalue=0.56			

Table 4: Clinical variables of patients with and without AKI in the laparoscopic group.

Variable	Non-AKI (n=13)	AKI (n=9)
Mean age (year)	56.9±3.2	67.3±4.9 *(P<0.0001)
Gender: Male/Female	7/6	6/3
Side: Right/Left	3/10	2/7
Tumor location Central/Peripheral	8/5	7/2
Mean Tumor Size (cm)	6.63±0.62	5.65±0.61* (P=0.0001)
Patients with comorbidities	13 (10 HPT; 5 DM; 1 IHD; 1 Nephrolithiasis; 5 dyslipidemia)	9 (7 HPT; 4 DM; 2 IHD; 4 Nephrolithiasis; 4 dyslipidemia)
Mean base line eGFR (ml/min)	82.7±5.1	50.43±5.09* (P<0.0001)
Mean blood loss (ml)	569±239	163.3±88.8* (P=0.0001)
Mean duration of pneumoperitoneum (min)	87.23±15.14	99.11±21.42
Serum creatinine (mg%)	Pre op'	1.005±0.05
	Post op' 8H	1.13±0.06
	Post op' 24H	1.14±0.07
		1.205±0.16* (P=0.0004)
		1.57±0.23* (P<0.0001)
		1.74±0.21* (P=0.001)

treated by the open approach. Our results suggest that older age and decreased baseline renal function may contribute to the development of AKI in patients managed by laparoscopic nephrectomy. One may assume that kidneys in elderly patients and compromised renal function are more vulnerable to the deleterious effect of increased intra-abdominal pressure. In a study by Cho A et al. [13] who evaluated 519 patients they found that age and GFR were predictors of post nephrectomy AKI. In their report patients who experienced post-operative AKI had a 4.24-fold higher risk of new onset CKD, P<0.001.

The duration of pneumoperitoneum during surgery by itself or amount of intra-operative blood loss were not predictors of AKI. Santos LS et al. [14] who studied the effects of pneumoperitoneum (15mmHg) during two and four hours in rats, reported no histologic changes of the kidneys. They used the same magnitude of intra-abdominal pressure that we have used during our laparoscopic procedures (12-14 mmHg). By contrast in a study published by Ben-Haim M et al. [15] that used higher pressure (20-25 mmHg) significant microscopic ischemic changes were observed. These data suggest that the magnitude of intra-abdominal pressure elevation may be important in causing renal injury.

We expected to find correlation between two novel biomarkers for AKI, namely NGAL and KIM-1 that were found to increase following kidney injury for various reasons. [16,17]. Such elevation could serve as a marker and may indicate the need to consider different

post-operative management such crystalloid support or use of nephroprotective agents. Our data indicate that pneumoperitoneum or the occurrence of AKI did not result in increased urinary level or different pattern concentration of these markers. Micali et al. [18] reported similar results. They compared laparoscopic and open procedure using N-acetyl-beta-D-glucosaminidase as a marker for kidney injury. No differences were noted in the urinary level of the marker between both groups. They concluded, that pneumoperitoneum is not associated with renal tubular injury. Others claim that after the release of pneumoperitoneum, renal function has recovered early and there were no signs of microscopic renal tubular damage [19].

Our study has several limitations including: 1-Small number of patients, especially in the open surgery; 2- A non-randomized study; 3- A single center study; 4- Some patients suffers from comorbidities (Diabetes, hypertension, peripheral vascular disease ect) that cannot be quantitated adequately; 5- We focused only on two biomarkers, based on previous literature and our own experience.

Conclusion

In the current study we were able to demonstrate that pneumoperitoneum used during laparoscopic nephrectomy affects immediate post-operative serum creatinine. The increased intra-abdominal pressure may result in higher rate of AKI compared with open procedure especially in elderly patients with compromised renal function. NGAL and KIM-1 urinary level were not affected by

the increased intra-abdominal pressure. To confirm these findings, a prospective randomized study with greater number of patients is needed.

Compliance with Ethical Standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

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