

Original Article

Does carbon dioxide pneumoperitoneum affect the renal function in donors following laparoscopic donor nephrectomy? A prospective study

Murali Vinodh, Vijaykumar Mohankumar, Arvind Ganpule, Banibrata Mukhopadhyay¹, Ravindra Sabnis, Mahesh Desai

Departments of Urology and ¹Biochemistry, Muljibhai Patel Urological Hospital, Nadiad, Gujarat, India

Address for Correspondence: Dr. Murali Vinodh, Muljibhai Patel Urological Hospital, Dr. Virendra Desai Road, Nadiad - 387 001, Gujarat, India. E-mail: vinodh.tmc@gmail.com

Abstract

CONTEXT: Although the technical feasibility of laparoscopic donor nephrectomy (LDN) has been established, concerns have been raised about the impaired renal function resulting from pneumoperitoneum and its short- and long-term effects. **AIMS:** We used urinary biomarkers of acute kidney injury including urinary neutrophil gelatinase-associated lipocalin (uNGAL) and urinary N-acetyl-beta-D-glucosaminidase (uNAG) to study the injury caused to the donor's retained kidney by pneumoperitoneum. **SETTINGS AND DESIGN:** This was a prospective cohort study of thirty consecutive patients who underwent LDN at our hospital. **SUBJECTS AND METHODS:** We measured urinary creatinine, uNAG and uNGAL at the time of induction of anaesthesia, at 1 h after starting surgery, at 5 min after clamping the ureter, at the time of skin closure and then at 4, 8 and 24 h after the surgery. **RESULTS:** The uNAG level showed a gradual increase from the start of the surgery and reached the peak at the time of the closure. Thereafter, there was a gradual fall in the level and reached to pre-operative level at 24 h post-surgery. Similarly, the uNGAL also showed a similar trend although it did not reach pre-operative value by 24 h. **CONCLUSIONS:** We objectively confirm that although there is acute injury to the retained kidney in the donor after LDN due to the CO₂ pneumoperitoneum, the renal function improves and reaches close to the pre-operative level within 24 h after surgery.

Key words: Acute kidney injury, laparoscopic donor nephrectomy, pneumoperitoneum

INTRODUCTION

Laparoscopic donor nephrectomy (LDN) is increasingly performed nowadays in many centres. Although the technical feasibility of LDN has been established, concerns have been raised about the impaired renal function resulting from pneumoperitoneum and its short- and long-term effects both in the recipient.^[1,2] Although animal studies have shown that abdominal gas insufflation does not impair renal function in the donor 1 year after LDN, there is scarcity in the literature supporting these findings in human studies.^[3] At present, serum creatinine, which is used to measure the glomerular filtration rate (GFR), is the most commonly used marker of renal function post-surgery. Unfortunately, serum creatinine is a delayed and unreliable indicator of acute kidney injury (AKI) as it is influenced by multiple non-renal factors, such as muscle mass, muscle metabolism, diet, medications and hydration status. Moreover, the serum creatinine level can take several hours or days to reach a new steady state and thus does not reflect the actual decrease in GFR in the acute setting as evidenced by the fact that it lags behind structural

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

For reprints contact: reprints@medknow.com

Cite this article as: Vinodh M, Mohankumar V, Ganpule A, Mukhopadhyay B, Sabnis R, Desai M. Does carbon dioxide pneumoperitoneum affect the renal function in donors following laparoscopic donor nephrectomy? A prospective study. *J Min Access Surg* 2017;13:200-4.

Date of submission: 18/05/2016, **Date of acceptance:** 06/01/2017

Access this article online	
Quick Response Code:	Website: www.journalofmas.com
	DOI: 10.4103/jmas.JMAS_117_16

changes that occur in the kidney during the early stage of AKI. Several studies have shown that urinary markers such as urinary neutrophil gelatinase-associated lipocalin (uNGAL) and urinary N-acetyl-beta-D-glucosaminidase (uNAG) are both sensitive and specific in identifying the AKI in various situations including in shock, post-cardiac surgery.^[4,5] The aim of this study is to understand if LDN has any effect on the long-term renal function in the other renal unit in the donor. We used urinary markers as surrogate indicators for ascertaining injury caused to the donor's kidney by the pneumoperitoneum and its long-term effects.

SUBJECTS AND METHODS

Study design

This was a prospective cohort study of thirty consecutive patients who underwent LDN between April 2013 and September 2013 at our hospital which is a tertiary care centre for urology where we so far have done 2615 renal transplants and 1205 LDN. Patients with body mass index (BMI) >30 kg/m², diabetes mellitus, severe atherosclerosis, asthma or chronic bronchitis, inflammatory bowel disease, hepatitis, hyperlipidaemia, alcohol ingestion and malignancy (lung, colorectal, breast, pancreas, leukaemia) were excluded from the study. The pre-operative parameters studied included estimated GFR (eGFR), haemoglobin, serum creatinine, urine routine and culture, urinary creatinine (uCr), uNAG and uNGAL. All participants consented to the study. The Institutional Review Board of our hospital approved the study protocol. Pre-operative computed tomography angiography was done in all the donors to assess the vascular anatomy. The kidney which was to be grafted was decided on the pre-operative assessment of the GFR and the vascular anatomy. LDN was done by one of the four urosurgeons with advanced laparoscopic training. All the donors were given adequate hydration intra-operatively and post-operatively.

Data collection

Medical records of study participants were reviewed prospectively to retrieve hospitalisation data, including baseline demographic characteristics; coexisting conditions and pre-operative renal variables including eGFR as measured by modification of diet in renal disease (MDRD) formula, haemoglobin, serum creatinine, urine routine and culture, uCr, uNAG and uNGAL. Then, urine NAG, NGAL, urine creatinine were measured before the start of surgery (at the induction of anaesthesia), at 1 h after starting surgery, at 5 min after clamping the ureter (this urine is mainly from the other retained kidney in the donor), at the end of the surgery (at the time of skin closure), 4, 8 and 24 h after the surgery. The time of surgery and the side of nephrectomy were

also noted. Post-operative parameters also included serum creatinine at 24 h, 30 days, 3 months and 1 year after surgery.

Measurement of urinary neutrophil gelatinase-associated lipocalin, urinary N-acetyl-beta-D-glucosaminidase and creatinine levels

The uNGAL level was measured by ELISA test using the kit manufactured by BioPorto[®] Diagnostics, Denmark (Category No. Kit 037). The uNAG was measured by colorimetric method using 4-nitrophenyl-glycoside substrates. The uCr was measured in Fully Automated Biochemistry Analyser CX5[®] PRO, Beckman Coulter, using the kit purchased from Beckman.

In this study, uNAG activity and uNGAL level were normalised to the uCr level to account for the difference in the relative amount of water extracted along the nephron. The various parameters were measured as mean with standard deviation and were studied by trend analysis.

RESULTS

A total of 30 consecutive donors undergoing consecutive nephrectomies were studied, out of which 5 patients were male and 25 patients were female. The mean age of the patients was 48.51 ± 10.15 years. The mean BMI, mean pre-operative serum creatinine and mean eGFR were 23.4 ± 3.56 kg/m², 0.63 ± 0.13 mg/dl and 107.24 ± 23.56 ml/min (MDRD formula), respectively. The mean time duration of the surgery and pneumoperitoneum were 157 ± 24.7 min and 145.6 ± 26.75 min, respectively [Table 1]. Three patients had post-operative fever (Clavien-Dindo Grade 1) which settled with conservative measures and one patient had post-operative chylous ascites which required laparoscopic clipping of the lymphatics (Clavien-Dindo Grade 3b).

The uNAG level normalised to the uCr showed a gradual increase from the start of the surgery (4.63 ± 4.64 IU/mg at the induction and 24.47 ± 11.86 IU/mg at 1 h after starting surgery) and reached the peak (40.86 ± 19.69 IU/mg) at the completion of the surgery. Thereafter, there was a gradual fall in the level (26.79 ± 19.14 IU/mg and 9.45 ± 6.57 IU/mg at 4 h and 8 h after surgery, respectively) and reached close to pre-operative level (6.07 ± 5.15 IU/mg) at 24 h post-surgery [Figure 1]. Similarly, the uNGAL level when normalised to urine creatinine showed a similar trend with gradual increase from the start (84.07 ± 127.83 IU/mg at the induction of surgery and 95.36 ± 102.52 IU/mg at 1 h after starting surgery), reaching peak level at the completion of the surgery (247.04 ± 163.83 IU/mg) after which there was a downward trend (196.59 ± 139.04 IU/mg and 113.15 ± 111.98 IU/mg at 4 h and 8 h after surgery, respectively)

although it did not reach pre-operative value by 24 h (110.25 ± 173.44 IU/mg) [Table 2]. There was no correlation made between the operative/pneumoperitoneum time and the level of these markers.

The mean post-operative serum creatinine at 24 h post-surgery was 0.91 ± 0.30 mg/dl, which improved to 0.86 ± 0.79 mg/dl at 1 month post-surgery and 0.81 ± 0.14 mg/dl at 3 months and 0.76 ± 0.23 mg/dl at 1 year after surgery [Table 3].

DISCUSSION

There are several concerns with the application of the laparoscopic approach for live renal donation. As it involves a healthy individual who is subjected to a major surgery to benefit another individual, safety of the donor is the first priority. Further, the kidney which is procured laparoscopically should provide excellent recipient graft outcomes. Since the initial report by Ratner *et al.*^[6] in 1995, LDN has become the standard technique in many transplant centres worldwide in view of the inherent advantages of laparoscopy including

less post-operative pain, better cosmesis and shorter convalescence, which will increase the number of kidney donations.^[7] However, laparoscopic procurement has other inherent problems including mechanical injury to the graft, longer warm ischaemia time and pneumoperitoneum, which may cause the primary dysfunction of transplanted kidneys.^[8] Although stable long-term graft function was demonstrated in retrospective studies at 1 year post-transplant in both open donor nephrectomy and LDN, it has been shown that recipients of laparoscopically procured kidneys have higher serum creatinine levels and a greater need for dialysis in the 1st weeks after transplantation.^[8-10] It has been shown that pneumoperitoneum causes increased intra-abdominal pressure which compresses the renal parenchyma and renal vein and can cause transient renal dysfunction due to impaired renal blood flow.^[1,11,12] However, there is scarcity in literature regarding the effect of pneumoperitoneum on the retained kidney in the donor. As serum creatinine is a delayed and unreliable indicator of AKI in the post-operative setting, we studied the effect of pneumoperitoneum on the donor renal function using non-invasive markers of renal ischaemia including uNGAL and uNAG.

Table 1: Demography of the donors

Number of donors (n)	30
Mean age (years)	48.51±10.15
Male:Female	5:25
Mean BMI (kg/m ²)	23.40±3.56
Preoperative mean eGFR (ml/min)	105.34±35.43
Mean serum creatinine (mg/dl)	0.62±0.13
Laterality - left:Right	27:3
Mean operating time (min)	157±24.16

eGFR: Estimated glomerular filtration rate, BMI: Body mass index

Table 2: Depicting the values of urinary N-acetyl-beta-D-glucosaminidase, urinary neutrophil gelatinase-associated lipocalin and urine creatinine

	uCr	uNAG (IU/mg)	uNGAL (IU/mg)
At induction	38.4±4.7	4.63±4.64	84.07±127.83
1 h after induction	1.92±0.84	24.47±11.86	95.36±102.52
5 min after clamp	1.62±0.66	31.41±14.84	185.38±220.64
End of surgery	2.10±0.87	40.86±19.69	247.04±163.83
4 h after surgery	3.36±1.95	26.79±19.14	196.59±139.04
8 h after surgery	18.49±25.67	9.45±6.57	113.15±111.98
24 h after surgery	37.79±38.89	6.07±5.15	110.25±173.44

uNGAL: Urinary neutrophil gelatinase-associated lipocalin, uNAG: Urinary N-acetyl-beta-D-glucosaminidase, uCr: Urinary creatinine

Table 3: Mean serum creatinine trend post surgery

	Serum creatinine (mg/dl)
Preop	0.62±0.13
24 hours post-surgery	0.91±0.30
1 month post surgery	0.86±0.79
3 months post surgery	0.81±0.14
1 year post surgery	0.76± 0.23

NGAL is a protein which is covalently bound to gelatinase and is mainly secreted from neutrophils and epithelial cells. It is concerned with the regulation of the tissue rebuilding mainly in the angiogenesis. Various organs which contain epithelial tissue including the kidneys produce a small amount of NGAL. However, its expression is rapidly increased in conditions that cause AKI when it can be detected in both the plasma and urine. It rises by 10-fold within only 3 h. After renal ischaemia, it has been found that there is rapid and massive induction of NGAL in renal tubular cells.^[13] Many other conditions including post-cardiac surgery, contrast-induced nephropathy, diabetic nephropathy and transplant rejection were also found to induce rapid increase in plasma NGAL (pNGAL) and

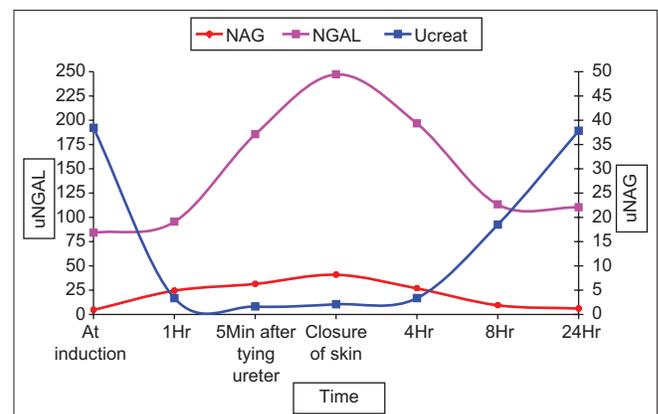


Figure 1: Graphical representation of the values of urinary creatinine, urinary neutrophil gelatinase-associated lipocalin and urinary N-acetyl-beta-D-glucosaminidase

uNGAL. Studies have also shown that uNGAL is probably more reflective for evaluation of the local renal injury than pNGAL^[14] and its increase in AKI precedes that of creatinine by 1–3 days and thus represents an early predictive biomarker for the development of AKI.^[15] Thus, uNGAL represents a sensitive non-invasive marker of renal ischaemia.

Wellwood *et al.* described the utility of uNAG activity as a marker of acute or chronic kidney injury more than 30 years ago.^[16] Then, in subsequent years, its role was limited to detect mild, sub-clinical renal tubular injury.^[17,18] More recently, it has been confirmed that increased excretion of uNAG was shown to be of diagnostic value for the early detection of AKI.^[18,19] NAG is mostly produced in proximal tubular epithelial cell lysosomes, and an increase in its urinary activity is a sensitive and reasonably specific measure of renal tubular damage, because it has a relatively large molecular weight (> 130 kD) which precludes its filtration by the glomerulus. It has been found in studies that in patients with established acute renal failure, uNAG activity is a useful surrogate marker for the severity of AKI and also has a prognostic utility similar to or better than conventionally used severity markers including urine output and serum creatinine level.^[20] uNAG activity remains elevated during active renal disease.

In animal studies done by Hazebroek *et al.*^[3] in rats, it has been found that abdominal gas insufflation did not impair renal function in the donor, 1 year after LDN, and there was no difference found in renal function or histomorphology between kidney grafts exposed to either pneumoperitoneum or gasless procedure.

The uNGAL and the uNAG measured at the start of the surgery and after 1 h signify the urine from both the kidneys, and there was increase in both the levels which indicate that there is acute tubular injury to both the kidneys. The third sample measured at 5 min after the ureteric clamping indicated the urine from the retained kidney in the donor and interestingly both the urinary markers increased exponentially and reached the peak at the sample taken at the end of the surgery suggesting that there is considerable injury caused to the donor retained kidney by the pneumoperitoneum. We could not find any correlation between the operative time and the level of these markers. However, the levels of both the biomarkers started to decrease thereafter suggesting that this effect is only transient and the levels almost but not completely reached to pre-operative levels by 24 h. Thus, the LDN, although causes a transient renal ischaemic injury, is safe in the long run and is advantageous for the donor in terms of residual renal function and decreased pain and early convalescence. The limitation of this study is that we had a small study group (30 donors) with

short follow-up. Although uNGAL is a very sensitive marker for AKI, uNAG has less specificity for AKI which has been viewed as another shortcoming of the study. Further prospective trials are required with larger numbers in the future.

CONCLUSIONS

In this study, we found that although there is acute injury to the retained kidney in the donor after LDN due to the CO₂ pneumoperitoneum, the renal function improves and reaches close to the pre-operative level within 24 h after surgery. Thus, LDN done by experts in high volume centres is safe to the donors in the long-term.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. McDougall EM, Monk TG, Wolf JS Jr., Hicks M, Clayman RV, Gardner S, *et al.* The effect of prolonged pneumoperitoneum on renal function in an animal model. *J Am Coll Surg* 1996;182:317-28.
2. Chiu AW, Chang LS, Birkett DH, Babayan RK. The impact of pneumoperitoneum, pneumoretroperitoneum, and gasless laparoscopy on the systemic and renal hemodynamics. *J Am Coll Surg* 1995;181:397-406.
3. Hazebroek EJ, de Bruin RW, Bouvy ND, Marquet RL, Bonthuis F, Bajema IM, *et al.* Long-term impact of pneumoperitoneum used for laparoscopic donor nephrectomy on renal function and histomorphology in donor and recipient rats. *Ann Surg* 2003;237:351-7.
4. Doi K, Urata M, Katagiri D, Inamori M, Murata S, Hisagi M, *et al.* Plasma neutrophil gelatinase-associated lipocalin in acute kidney injury superimposed on chronic kidney disease after cardiac surgery: A multicenter prospective study. *Crit Care* 2013;17:R270.
5. Fouda M, Sherif HM, Shehata M, Ibrahim A. Early expression of urinary neutrophil gelatinase-associated lipocalin biomarker predicts acute kidney injury complicating circulatory shock. *Egypt J Crit Care Med* 2013;1:79-86.
6. Ratner LE, Ciseck LJ, Moore RG, Cigarroa FG, Kaufman HS, Kavoussi LR. Laparoscopic live donor nephrectomy. *Transplantation* 1995;60:1047-9.
7. Ratner LE, Hiller J, Sroka M, Weber R, Sikorsky I, Montgomery RA, *et al.* Laparoscopic live donor nephrectomy removes disincentives to live donation. *Transplant Proc* 1997;29:3402-3.
8. Nogueira JM, Cangro CB, Fink JC, Schweitzer E, Wiland A, Klassen DK, *et al.* A comparison of recipient renal outcomes with laparoscopic versus open live donor nephrectomy. *Transplantation* 1999;67:722-8.
9. Flowers JL, Jacobs S, Cho E, Morton A, Rosenberger WF, Evans D, *et al.* Comparison of open and laparoscopic live donor nephrectomy. *Ann Surg* 1997;226:483-9.
10. Ratner LE, Montgomery RA, Maley WR, Cohen C, Burdick J, Chavin KD, *et al.* Laparoscopic live donor nephrectomy: The recipient. *Transplantation* 2000;69:2319-23.
11. Kirsch AJ, Hensle TW, Chang DT, Kayton ML, Olsson CA, Sawczuk IS. Renal effects of CO₂ insufflation: Oliguria and acute renal dysfunction in a rat pneumoperitoneum model. *Urology* 1994;43:453-9.
12. Chang DT, Kirsch AJ, Sawczuk IS. Oliguria during laparoscopic surgery. *J Endourol* 1994;8:349-52.
13. Xu S, Venge P. Lipocalins as biochemical markers of disease. *Biochim Biophys Acta* 2000;1482:298-307.

Vinodh, *et al.*: Effect of pneumoperitoneum on donors in lap donor nephrectomy

14. Kimpers P, Hafer C, Lukasz A, Lichtinghagen R, Brand K, Fliser D, *et al.* Serum neutrophil gelatinase-associated lipocalin at inception of renal replacement therapy predicts survival in critically ill patients with acute kidney injury. *Crit Care* 2010;14:R9.
15. Haase M, Bellomo R, Devarajan P, Schlattmann P, Haase-Fielitz A; NGAL Meta-analysis Investigator Group. Accuracy of neutrophil gelatinase-associated lipocalin (NGAL) in diagnosis and prognosis in acute kidney injury: A systematic review and meta-analysis. *Am J Kidney Dis* 2009;54:1012-24.
16. DeLong ER, DeLong DM, Clarke-Pearson DL. Comparing the areas under two or more correlated receiver operating characteristic curves: A nonparametric approach. *Biometrics* 1988;44:837-45.
17. Wellwood JM, Ellis BG, Price RG, Hammond K, Thompson AE, Jones NF. Urinary N-acetyl- beta-D-glucosaminidase activities in patients with renal disease. *Br Med J* 1975;3:408-11.
18. Kang HK, Kim DK, Lee BH, Om AS, Hong JH, Koh HC, *et al.* Urinary N-acetyl-beta-D-glucosaminidase and malondialdehyde as a markers of renal damage in burned patients. *J Korean Med Sci* 2001;16:598-602.
19. Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: Evaluation of renal function. *Ann Thorac Surg* 1999;68:493-8.
20. Liangos O, Perianayagam MC, Vaidya VS, Han WK, Wald R, Tighiouart H, *et al.* Urinary N-acetyl-beta-(D)-glucosaminidase activity and kidney injury molecule-1 level are associated with adverse outcomes in acute renal failure. *J Am Soc Nephrol* 2007;18:904-12.

