CLINICS

CLINICAL SCIENCE

Protective response in renal transplantation: no clinical or molecular differences between open and laparoscopic donor nephrectomy

Christiano Machado,[I] Denise Maria Avancini Costa Malheiros,[II] Ari Adamy,[I] Luiz Sergio Santos,[I] Agenor Ferreira da Silva Filho,[I] William Carlos Nahas,[III] Francine Brambate Carvalhinho Lemos[III]

[I] Hospital de Caridade, Irmandade Santa Casa de Misericórdia de Curitiba, Division of Urology, Curitiba/PR, Brazil. [II] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Department of Pathology, São Paulo/SP, Brazil. [III] Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo, Renal Transplantation Section, Division of Urology, São Paulo/SP, Brazil.

OBJECTIVE: Prolonged warm ischemia time and increased intra-abdominal pressure caused by pneumoperitoneum during a laparoscopic donor nephrectomy could enhance renal ischemia reperfusion injury. For this reason, laparoscopic donor nephrectomy may be associated with a slower graft function recovery. However, an adequate protective response may balance the ischemia reperfusion damage. This study investigated whether laparoscopic donor nephrectomy modified the protective response of renal tissue during kidney transplantation.

METHODS: Patients undergoing live renal transplantation were prospectively analyzed and divided into two groups based on the donor nephrectomy approach used: 1) the control group, recipients of open donor nephrectomy (n = 29), and 2) the study group, recipients of laparoscopic donor nephrectomy (n = 26). Graft biopsies were obtained at two time points: T-1 = after warm ischemia time and T+1 = 45 minutes after kidney reperfusion. The samples were analyzed by immunohistochemistry for the Bcl-2 and HO-1 proteins and by real-time polymerase chain reaction for the mRNA expression of Bcl-2, HO-1 and vascular endothelial growth factor.

RESULTS: The area under the curve for creatinine and delayed graft function were similar in both the laparoscopic and open groups. There was no difference in the protective gene expression between the laparoscopic donor nephrectomy and open donor nephrectomy groups. The protein expression of HO-1 and Bcl-2 were similar between the open and laparoscopic groups. Furthermore, the gene expression of B-cell lymphoma 2 correlated with the warm ischemia time in the open group ($p = 0.047$) and that of vascular endothelial growth factor with the area under the curve for creatinine in the laparoscopic group ($p = 0.01$).

CONCLUSION: The postoperative renal function and protective factor expression were similar between laparoscopic donor nephrectomy and open donor nephrectomy. These findings ensure laparoscopic donor nephrectomy utilization in renal transplantation.

KEYWORDS: Apoptosis; Gene Expression; Kidney Transplantation; Laparoscopy; Reperfusion Injury.

Machado C, Malheiros DM, Adamy A, Santos LS, Silva Filho AF, Nahas WC, et al. Protective response in renal transplantation: no clinical or molecular differences between open and laparoscopic donor nephrectomy. Clinics. 2013;68(4):483-488.

Received for publication on October 22, 2012; **First review completed on** November 18, 2012; **Accepted for publication on** December 11, 2012

E-mail: christianombr@yahoo.com

Tel.: 55 41 3252-9943

INTRODUCTION

Laparoscopic donor nephrectomy (LDN) has gained widespread acceptance because of diminished donor morbidity compared with the open approach. LDN has better pain control, shorter hospital stays, faster return to normal activity and improved cosmesis (1-4). However, laparoscopically harvested kidneys may regain normal function more slowly than open-recruited organs, and their long-term graft survival is debatable (5). Prolonged warm ischemia time (WIT) is usually observed after laparoscopic surgery, but its effect on graft function is not completely understood. Furthermore, experimental studies have demonstrated that laparoscopy could increase renal ischemia-reperfusion injury (IRI) after renal transplantation (6,7).

Renal IRI is an inherent event in renal transplantation, and the extent of graft damage reflects the balance between deleterious events and protective factors. One protective factor is heme-oxygenase-1, a heat shock protein that participates in vascular tone control and has anti-apoptotic,

No potential conflict of interest was reported.

DOI: 10.6061/clinics/2013(04)08

anti-inflammatory and antioxidant functions (8). Another important factor involved in the protective response is VEGF, a potent angiogenic factor that has been shown to be crucial in preserving vascular integrity and microcirculation repair (9). Bcl-2 is an anti-apoptotic protein that may play a role in renal transplantation by preventing apoptosis during ischemia. In deceased donors, a diminished mRNA expression of HO-1, VEGF and Bcl-2 had been previously observed compared with living donors. Furthermore, a correlation between renal function and HO-1 and VEGF was noted, which reinforced their protective roles in renal transplantation (10).

To our knowledge, no study has investigated IRI-protective factors during laparoscopy. Therefore, we investigated whether LDN could affect the protective response of live renal transplantation.

PATIENTS AND METHODS

Patient population

Fifty-five patients who underwent living donor transplants from October 2009 to September 2011 at our institution were included in the analysis. The patients were further divided into two groups based on the donor nephrectomy approach that was used. The control group comprised 29 recipients who received kidneys retrieved by open donor nephrectomy (ODN), and the study group included 26 recipients of kidneys retrieved by LDN. This study was approved by the local ethics committee, and each patient provided informed consent. All of the patients included in the analysis received intraoperative induction therapy with anti-thymocyte globulin or basiliximab and a maintenance immunosuppression regimen with tacrolimus, mycophenolate and prednisone.

Warm ischemia time was defined as the interval between the renal artery occlusion and the kidney immersion in ice slush. Renal function was evaluated by the serum creatinine level on days one to seven, day 30 and the third and sixth months after transplantation. The area under the curve for creatinine from the first to the ninetieth postoperative days was used to observe the creatinine decline. Delayed graft function (DGF) was defined as the need for dialysis during the first week after transplantation, and functional delayed graft function (FDGF) was defined as the absence of a decrease in the serum creatinine level of at least 10% per day for three consecutive days in the first week after renal transplantation.

Renal allograft biopsies were obtained at two time points: after WIT (T-1) and 45 minutes after kidney reperfusion (T+1). The biopsies were divided into two pieces, with one used for immunohistochemistry and the other for RNA extraction.

Real-time polymerase chain reaction (PCR)

The mRNA expressions of Bcl-2, VEGF and HO-1 in renal tissue were analyzed with real-time PCR using a Taqman master mix (Applied Biosystems, Foster City, CA, USA) and the 7500 Real Time PCR system (Applied Biosystems, Foster City, CA, USA). The level of the different RNA factors in the renal tissue was normalized to the housekeeping gene 18S. The primers utilized were developed by Applied Biosystems. The sequences of the 5′ primers used were 18S CCATTGGAGGGCAAGTCTGGTGCCA, Bcl-2 TAACGGAGGCTGGGATGCCTTTGTG, VEGF CAAGAAAAATGTGACAAGCCGAGGC and HO-1 GACGGCTTCAAGCTGGTGATGGCCT. The cycle number at which the reporter fluorescence crossed the threshold (C_T value) was used as a quantitative measurement of the copies of the target in any sample, and the mean of the normalization of these values ($\Delta C_T = C_T$ target gene-C_T housekeeping gene) was used for a comparison between groups. We emphasize that the greater the ΔC_T, the lower the gene expression. We compared the laparoscopic group samples at time points T-1 and T+1 with the respective open group time points.

Immunohistochemistry

The renal biopsies were immersed in Dubosq solution for 30 minutes and fixed in 10% buffered formalin, embedded in paraffin, and sectioned. The slides were processed for routine histology. The protein expressions of Bcl-2 and HO-1 were determined by immunohistochemistry in the renal biopsy samples. The primary antibodies used were mouse monoclonal anti-human HO-1 (Clone GTS-1; Novus Biological, Littleton City, CO, USA) and mouse monoclonal anti-human Bcl-2 (Clone 3.1, Novocastra, Newcastle upon Tyne City, UK). Each primary antibody utilized was previously titered in human renal tissue samples. A semiquantitative analysis was performed.

Statistical analysis

We used Fisher's exact test for the categorical variables. Continuous variables were reported as the mean ± standard deviation and compared using Student's t-test and an analysis of variance (ANOVA). The relationships between variables were assessed with Pearson's correlation coefficient. All of the tests were two-tailed, and $p<0.05$ was considered statistically significant.

RESULTS

The demographics and clinical characteristics of the recipients and donors are shown in Table 1. There were no significant differences between the two groups regarding the baseline characteristics.

Multiple arteries were observed in four patients (14%) in the open group and in three patients (12%) in the laparoscopic group. The mean WIT was significantly longer in the laparoscopic group compared with the open group (194 *vs.* 132 seconds; $p = 0.005$). DGF was observed in three patients, one (3%) in the open group and two (8%) in the laparoscopic group, with no significant difference ($p = 0.60$). FDGF occurred in four patients in the open group and in three cases in the laparoscopic group (14% *vs.* 12%, $p = 0.99$).

Renal function after transplantation, as evaluated by the serum creatinine levels and the area under the curve of serum creatinine (AUCcr), was similar between the open (mean AUCcr = 122) and laparoscopic groups (mean AUCcr = 133, $p = 0.33$) (Figure 1). WIT was not associated with DGF, FDGF or AUCcr.

mRNA expression by Real-time PCR

Bcl-2. Thirty-nine samples from 24 patients were analyzed for the mRNA expression of Bcl-2. In the open group, 13 samples were evaluated at time point T-1 and 11 samples after reperfusion at T+1. In the laparoscopic group, nine samples were evaluated at T-1 and six samples at T+1. The comparison between the kidneys retrieved by open and laparoscopic nephrectomy showed no significant difference at time points T-1 (open, mean $\Delta C_T = 10.29$ and

Table 1 - Recipient and donor characteristics at transplantation time.

RECIPIENTS		Open	Laparoscopic	*p*-value
No. patients		29	26	
Mean age ± SD		43 ± 12	44 ± 14	0.71
Gender female (%)		16/29 (55%)	13/26 (50%)	0.79
BMI ± SD		23.9 ± 4.1	24.3 ± 4.3	0.71
Induction suppression anti-IL2R		23/29 (79%)	20/26 (77%)	0.78
Immunosuppression at three months				
Pred+Tacro+MP		25/29 (86%)	24/26 (92%)	0.57
Prior Transfusion		0.90 ± 0.33	0.93 ± 0.64	0.71
Prior pregnancy		2 ± 2	3 ± 2	0.23
Re-transplant		0 (0%)	2/26 (8%)	0.22
HLA Mismatches		3.9 ± 1.9	2.9 ± 2.1	0.15
PRA	<10%	19/27 (70%)	15/23 (65%)	0.34
	10-50%	6/27 (22%)	5/23 (22%)	
	>50%	1/27 (4%)	3/23 (13%)	
DONORS				
Mean age ± SD		35 ± 10	36 ± 10	0.74
Donor type	RLD	24/29 (83%)	20/26 (77%)	0.74
	URLD	5/29 (17%)	6/26 (23%)	
Age >50 y		2/29 (7%)	2/29 (8%)	0.99
Donor gender (%)	Female	20/29 (69%)	21/26 (81%)	0.37
% Female donor/		12/29 (41%)	12/26 (46%)	0.39
Mean BMI ± SD		24.5 ± 4	26.2 ± 3	0.12

BMI = body mass index; anti-IL2R = anti-interleucin-2 receptor (daclizumab/basiliximab); Pred = prednisone, Tacro = tacrolimus, MPS = mycophenolate sodium; PRA = panel-reactive antibody RLD = related living-donor URLD = unrelated living-donor.

laparoscopic, mean $\Delta C_T = 9.98$, $p = 0.75$) and T+1 (open, mean $\Delta C_T = 10.94$ and laparoscopic, mean $\Delta C_T = 11.25$, $p = 0.82$). To investigate any kinetic change in the mRNA during the nephrectomy procedure, we compared the Bcl-2 mRNA expression at T-1 and T+1 for each type of procedure. The comparison showed no differences between T-1 and T+1 for both the open ($p = 0.77$) and laparoscopic ($p = 0.09$) procedures.

Vascular endothelial growth factor (VEGF). Thirty-five samples from 24 patients were analyzed for the mRNA expression. In the open group, 11 samples were evaluated at T-1 and nine samples after reperfusion at T+1. In the laparoscopic group, eight samples were analyzed at T-1 and seven samples at T+1. There were no significant differences between the open and laparoscopic groups at T-1 (open, mean $\Delta C_T = 10.66$, and laparoscopic, mean $\Delta C_T = 10.38$, $p = 0.64$) and T+1 (open, mean $\Delta C_T = 11.11$ and laparoscopic, mean $\Delta C_T = 11.71$, $p = 0.52$). When the two time points (T-1 and T+1) were compared in each group, no differences were observed (open, $p = 0.70$ and laparoscopic, $p = 0.26$).

Heme-oxygenase 1 (HO-1). From 24 patients, 39 samples were quantified for the mRNA expression levels of HO-1. In the open group, 13 samples were evaluated at T-1, and 10 samples at T+1. In the laparoscopic group, 9 samples were evaluated at T-1, and 7 samples after reperfusion (T+1). No difference was observed for the comparison of the two groups at T-1 (open: mean $\Delta C_T = 10.86$ and laparoscopic: mean $\Delta C_T = 10.11$; $p = 0.57$) and T+1 (open: mean $\Delta C_T = 10.42$ and laparoscopic: mean $\Delta C_T = 10.90$; $p = 0.76$). No differences were observed for the comparison of the two time points ($p = 0.45$ and $p = 0.40$ for the open and laparoscopic groups, respectively).

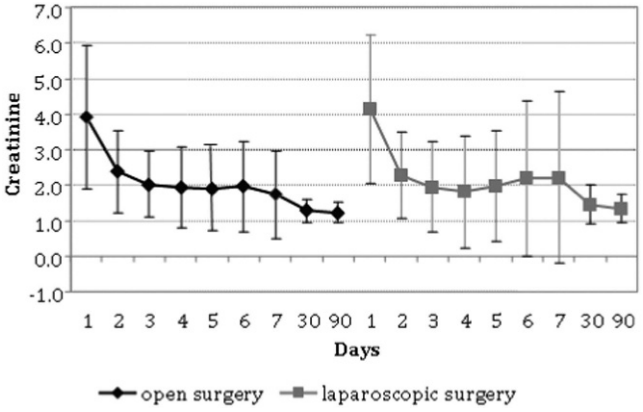

Figure 1 - Curve for the serum creatinine level decrease during the first days after transplantation.

Histological analysis and protein expression by immunohistochemistry

During the preliminary histological analysis, we found the histological characteristics of acute tubular necrosis in 44% of samples in the open group and in 45% in the laparoscopic group. Only one patient in the open group had severe acute tubular necrosis. In the remaining samples, the changes were mild.

A total of 86 samples were evaluated by immunohistochemistry for the protein expression of Bcl-2 and Heme oxygenase-1.

Bcl-2 protein expression. Bcl-2 was expressed mainly at the tubular epithelial cells (Figure 2). Eighty-six biopsy specimens were available from forty-four patients for the evaluation of Bcl-2 protein expression. Compared with the open nephrectomy, the Bcl-2 protein expression in the laparoscopic group appeared to be increased. However, the difference was not significant. At the reperfusion time point T+1, there was a decrease in the mean expression of Bcl-2 in both groups, but the differences were not significant (Figure 3).

Heme oxygenase-1 (HO-1) protein expression. Thirty-eight samples from twenty patients were evaluated at two time points. At T-1, 11 samples from the open group were evaluated, and 7 (63.6%) were positive for HO-1. In the laparoscopic group, seven samples were analyzed with one positive case (14.3%) ($p = 0.07$). After reperfusion (T+1), 11 samples were analyzed in the open group, with 5 (45.5%) positive for HO-1. In the 9 laparoscopic samples, 6 (66.7%) expressed the HO-1 protein ($p = 0.41$). The HO-1 protein expression at T+1 (after reperfusion) tended to increase compared with T-1 in the laparoscopic group ($p = 0.06$). No significant difference in HO-1 expression was observed between the two time points in the open group ($p = 0.67$) (Table 2).

Relationship between mRNA and protein expression and the clinical parameters

When we analyzed the mRNA expression findings and their correlation with the clinical and surgical features, we noticed a correlation between WIT and ΔC_T Bcl-2 in the open group at the moment of kidney retrieval (T-1) (Pearson $r = 0.582$, $p = 0.047$). This correlation indicated that in open nephrectomy, a longer warm ischemia time was associated

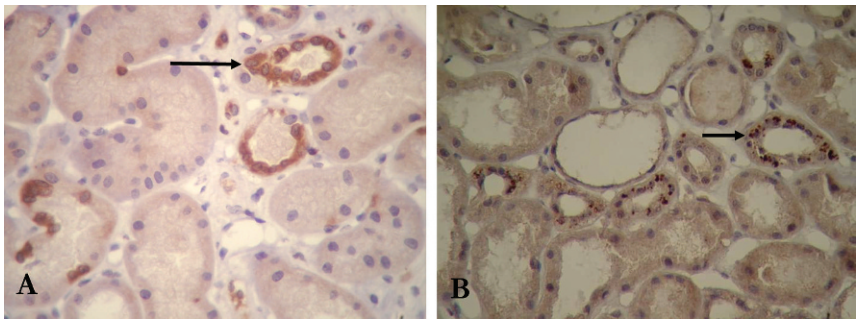

Figure 2 - Immunohistochemical staining for Bcl-2 (A) and HO-1 (B), expressed predominantly in the renal tubule cells.

with a lower expression level of the Bcl-2 mRNA. The AUCcr was negatively correlated with the ΔC_T of VEGF in the laparoscopic group after reperfusion (Pearson $r = -0.919$, $p = 0.01$), i.e., a slower decline of creatinine correlated with a higher expression level of the VEGF mRNA in the laparoscopic group (Figure 4).

DISCUSSION

In the present study, the protective response of the renal tissue was investigated in the context of ischemia reperfusion injury during a laparoscopic kidney nephrectomy. Compared with conventional open nephrectomy, the patients transplanted with kidneys retrieved by a laparoscopic procedure had similar renal functions after transplantation, and differences were not observed in the protective response.

The most evident clinical manifestation of tissue damage caused by renal ischemia reperfusion injury is the occurrence of delayed graft function (DGF), which impacts both short and long-term graft survival (11,12). In several centers, the DGF in living donor transplantation is approximately 5%, which is similar to our findings (13). In our study, the incidence of DGF was 3% in the open nephrectomy group and 8% in the laparoscopic group; these rates were not significantly different. In addition to the DGF criteria, we used other parameters to better evaluate any impact from nephrectomy on renal function, such as the decline in creatinine for three consecutive days after the transplantation and the area under the curve for creatinine. This last parameter could be useful for identifying any mild changes in the serum creatinine decline during the first weeks after transplantation. Analyzing all of these parameters, we observed no differences in the allograft renal functions of laparoscopic and open nephrectomy recipients. Similarly, a systematic review of the literature revealed a comparable recovery of renal function and DGF incidence between open and laparoscopic renal transplantations (14).

The loss of tubular epithelial cells is the main histological finding of the tissue damage caused by renal ischemia-reperfusion injury. In our study, acute tubular necrosis was observed in 44% of the patients in the open nephrectomy group and in 45% in the laparoscopic group. The pathological analysis showed a mild lesion, with only one patient having a severe lesion that developed into DGF. A histopathological evaluation of the donor kidneys procured by laparoscopic nephrectomy was previously performed by Shimizu et al. (15). The authors found that 54% of the specimens had subcapsular cortical damage, which was much more intense in the hand-assisted laparoscopy group; this damage was most likely caused by pneumoperitoneum and mechanical injury during surgical manipulation. In the Shimizu et al. study, the description of acute tubular necrosis was analyzed together with the congestion of glomerular and peritubular capillaries. We did not find these vascular lesions in our groups, but the high percentage of acute tubular necrosis appeared to be a relevant finding even without significant renal function changes.

The inflammatory response during ischemia-reperfusion was mediated by different mechanisms and molecules. In our samples, we analyzed the gene expression levels of INFγ, TNFα and IL-6, and we did not observe any differences between open and laparoscopic nephrectomy

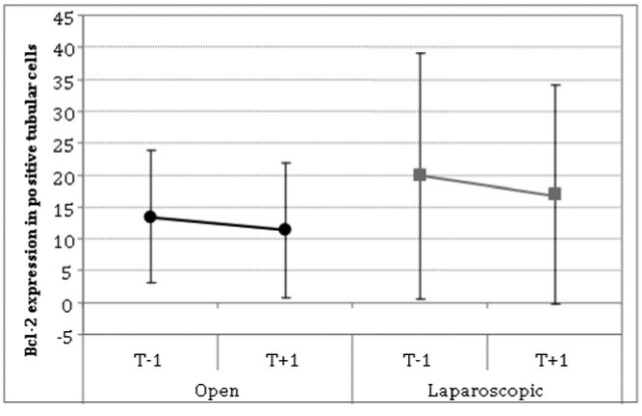

Figure 3 - Comparison of the mean protein expression of Bcl-2 ± 1 standard deviation. Open group: T-1 = 13 ± 10 and T+1 = 11 ± 11; Laparoscopic group: T-1 = 20 ± 19 and T+1 = 17 ± 17 (p = NS, ANOVA).

Table 2 - Comparison of the HO-1 protein expression between the LDN and ODN groups at two time points.

Groups	T-1	T+1	*p*-value
ODN	7/11 (63.6%)	5/11 (45.5%)	0.67
LDN	1/7 (14.3%)	6/9 (66.7%)	0.06
	n = 18	n = 20	
p-value	0.07	0.41	

LDN = laparoscopic donor nephrectomy.
ODN = open donor nephrectomy.

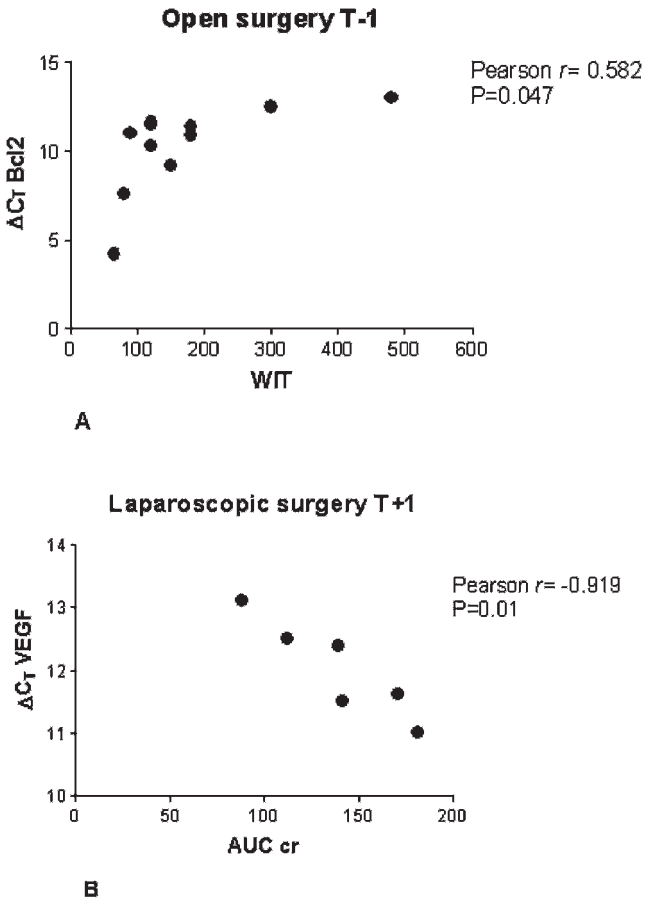

Figure 4 - A) Correlation between the Bcl-2 mRNA expression levels after kidney retrieval and the warm ischemia time in open surgery. **B)** Correlation between the VEGF mRNA expression levels after reperfusion and the area under the curve of the serum creatinine level in the laparoscopic surgery group.

(data not shown). Based on previous reports highlighting the importance of the protective response to counterbalance the injury during ischemia-reperfusion, we investigated this adaptive response during the laparoscopic nephrectomy (16-18). We investigated the protective molecules HO-1 and VEGF. Heme oxygenase-1, which is induced by hypoxia, plays a critical role in the renal protective response because of its anti-apoptotic, anti-inflammatory and antioxidant properties and its vascular tone regulation (19). As an important angiogenic factor, VEGF is essential for maintaining peritubular capillaries, which maintain adequate renal tubule and interstitium blood supplies (20). Experimental studies have observed VEGF reduction after ischemia reperfusion injury, particularly when the kidney was submitted to a prolonged period of ischemia (21,22). In our study, we did not find any difference in the HO-1 and VEGF gene transcript levels between the open and laparoscopic groups after the warm ischemia time or after 45 minutes of reperfusion. Note that a further change in the mRNA expression cannot be excluded and that the duration of 45 minutes could be still too early to identify any different patterns between the groups. In this regard, we observed that a higher VEGF mRNA expression in the laparoscopic group after reperfusion was associated with a slower decrement of serum creatinine after transplantation, which suggested that in situations with more intense injury, an increase in VEGF may represent an attempt to repair damaged tissue and that this protective gene was not inhibited during the laparoscopic surgery.

Concerns about a prolonged warm ischemia time (WIT) and its effect on renal allograft function always existed in the laparoscopic era. Nogueira et al. (23) found a prolonged WIT as a risk factor for delayed graft function in the grafts of laparoscopic donors. In contrast, Buzdon et al. (24) and Simforoosh et al. (25) did not find decreased renal function as a consequence of longer WIT. In our series, the laparoscopic group had a longer WIT than the open group but did not have higher rates of DGF or functional DGF. Furthermore, no association between the WIT and serum creatinine decline was observed. However, the WIT was weakly associated with diminished Bcl-2 gene expression after kidney open retrieval, which could reflect a decreased protective response in open surgery when the kidney is exposed to periods of prolonged oxygen deprivation. In the laparoscopic group, this association was not observed and may reflect ischemic preconditioning, as the kidney is continuously exposed to parenchyma compression caused by pneumoperitoneum pressure. In animals, it has been demonstrated that hypoxic preconditioning might activate HIF-1α, leading to an increase in the Bcl-2 protein expression (26).

In laparoscopy, apoptosis has been shown to increase in rats that are submitted to different pneumoperitoneum gradients of pressure, which suggests that an elevation of intra-abdominal pressure could increase the ischemia-reperfusion injury and cause apoptosis (27). However, in our study, we found no differences in the gene and protein expression of Bcl-2 in the laparoscopic and open groups. Therefore, a negative effect of the pneumoperitoneum, with respect to renal apoptosis, was not observed.

Although our study analyzed a limited sample size, we were careful to evaluate different moments of tissue injury during the nephrectomy and to also analyze expression at both the gene and protein levels. The immunohistochemistry analysis revealed Bcl-2 and HO-1 protein expression in the tubular epithelial cells with no differences between the open and laparoscopic groups. However, there were decreases in the mean Bcl-2 protein and gene expressions after reperfusion; these decreases were not significantly different. During the first time-point biopsy, we observed a trend towards lower protein expression for the HO-1 protein expression in the laparoscopic group, whereas after reperfusion, there was a trend towards increased HO-1 protein expression. Interestingly, other authors have reported similar results. Ollinger et al. (28) observed a quantitative increase in the HO-1 expression after reperfusion in deceased renal transplantation biopsies; this increase was associated with delayed graft function and higher increases in the HO-1 protein levels from pre- to post-reperfusion.

Finally, this investigation analyzed aspects of renal IRI in LDN that have not been previously studied. The renal function of the recipients of LDN and ODN and protective factors of renal ischemia reperfusion injury in the renal tissue of LDN and ODN were similar. Therefore, these findings are important for reinforcing laparoscopic nephrectomy utilization in live renal transplantation.

ACKNOWLEDGMENTS

Funding for this study was provided by Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP).

AUTHOR CONTRIBUTIONS

Machado C contributed to the conception and design, data acquisition, analysis and interpretation, drafting of the manuscript and statistical analysis. Malheiros DM contributed to the data acquisition and technical support. Adamy A contributed to the data interpretation, drafting of the manuscript, critical revision of the manuscript for important intellectual content and statistical analysis. Santos LS and Silva Filho AF contributed to the data acquisition and critical revision of the manuscript for important intellectual content. Nahas WC contributed to the conception and design, data acquisition, analysis and interpretation and obtained funding. Lemos FB contributed to the conception and design, data acquisition, analysis and interpretation, drafting of the manuscript, statistical analysis and technical support.

REFERENCES

1. Ratner LE, Kavoussi LR, Schulam PG, Bender JS, Magnuson TH, Montgomery R. Comparison of laparoscopic live donor nephrectomy versus the standard open approach. Transplant proc. 1997;29(1-2):138-9, http://dx.doi.org/10.1016/S0041-1345(96)00037-1.
2. Andersen MH, Mathisen L, Oyen O, Edwin B, Digernes R, Kvarstein G, et al. Postoperative pain and convalescence in living kidney donors-laparoscopic versus open donor nephrectomy: a randomized study. Am J Transplant. 2006;6(6):1438-43.
3. Kim FJ, Ratner LE, Kavoussi LR. Renal Transplantation: Laparoscopic Live Donor Nephrectomy. Urol Clin North Am. 2000;27(4):777-85, http://dx.doi.org/10.1016/S0094-0143(05)70125-7.
4. Khauli RB E-HY, Hussein M, Dagher FJ, Medawar W, Houjaij A, et al. A controlled sequential evaluation of open donor nephrectomy versus classical and modified laparoscopic donor nephrectomy: an update. Transplant Proc. 2005;37(7):2944-6, http://dx.doi.org/10.1016/j.transproceed.2005.08.016.
5. Troppmann C, Ormond DB, Perez RV. Laparoscopic (vs. Open) Live Donor Nephrectomy: A UNOS Database Analysis of Early Graft Function and Survival. Am J Transplant. 2003;3(10):1295-301.
6. Burgos F, Pascual J, Briones G, Cuevas B, Villafruela J, Correa C, et al. Influence of laparoscopic live donor nephrectomy in ischemia–reperfusion syndrome and renal function after kidney transplantation: an experimental study. Transplant Proc. 2003;35(5):1664-5, http://dx.doi.org/10.1016/S0041-1345(03)00622-5.
7. Kurian SM, Flechner SM, Kaouk J, Modlin C, Goldfarb D, Cook DJ, et al. Laparoscopic Donor Nephrectomy Gene Expression Profiling Reveals Upregulation of Stress and Ischemia Associated Genes Compared to Control Kidneys. Transplantation. 2005;80(8):1067-71, http://dx.doi.org/10.1097/01.tp.0000176485.85088.f7.
8. Holzen JP, August C, Bahde R, Minin E, Lang D, Heidenreich S, et al. Influence of heme oxygenase-1 on microcirculation after kidney transplantation. J Surg Res. 2008;148(2):126-35, http://dx.doi.org/10.1016/j.jss.2007.10.007.
9. Masuda Y, Shimizu A, Mori T, Ishiwata T, Kitamura H, Ohashi R, et al. Vascular Endothelial Growth Factor Enhances Glomerular Capillary Repair and Accelerates Resolution of Experimentally Induced Glomerulonephritis. Am J Pathol. 2001;159(2):599-608.
10. Lemos FBC, Ijzermans JN, Zondervan P, Peeters AMA, Van Den Engel S, Mol WM, et al. Differential expression of heme oxygenase-1 and vascular endothelial growth factor in cadaveric and living donor kidneys after ischemia-reperfusion. J Am Soc Nephrol. 2003;14(12):3278-87, http://dx.doi.org/10.1097/01.ASN.0000098683.92538.66.
11. Siedlecki A, Irish W, Brennan DC. Delayed graft function in the kidney transplant. Am J Transplant. 2011;11(11):2279-96.
12. Yarlagadda SG, Coca SG, Formica RN Jr, Poggio ED, Parikh CR. Association between delayed graft function and allograft and patient survival: a systematic review and meta-analysis. Nephrol Dial Transplant. 2009;24(3):1039-47.
13. Perico N, Cattaneo D, Sayegh MH, Remuzzi G. Delayed graft function in kidney transplantation. The Lancet. 2004;364(9447):1814-27, http://dx.doi.org/10.1016/S0140-6736(04)17406-0.
14. Greco F, Hoda MR, Alcaraz A, Bachmann A, Hakenberg OW, Fornara P. Laparoscopic living-donor nephrectomy: analysis of the existing literature. Eur Urol. 2010;58(4):498-509, http://dx.doi.org/10.1016/j.eururo.2010.04.003.
15. Shimizu T, Tanabe K, Ishida H, Toma H, Yamagushi Y. Histopathological evaluation of 0-h biopsy specimens of donor kidney procured by laparoscopic donor nephrectomy. Clin Transplant. 2004;18(Suppl.11):24-8, http://dx.doi.org/10.1111/j.1399-0012.2004.00243.x.
16. Exner M, Böhmig GA, Schillinger M, Regele H, Watschinger B, Hörl WH, et al. Donor heme oxygenase-1 genotype is associated with renal allograft function1. Transplantation. 2004;77(4):538-42, http://dx.doi.org/10.1097/01.TP.0000113467.36269.F8.
17. Faleo G, Neto JS, Kohmoto J, Tomiyama K, Shimizu H, Takahashi T, et al. Carbon monoxide ameliorates renal cold ischemia-reperfusion injury with an upregulation of vascular endothelial growth factor by activation of hypoxia-inducible factor. Transplantation. 2008;85(12):1833-40, http://dx.doi.org/10.1097/TP.0b013e31817c6f63.
18. Ferenbach DA, Kluth DC, Hughes J. Hemeoxygenase-1 and renal ischaemia-reperfusion injury. Nephron Exp Nephrol. 2010;115(3):e33-7, http://dx.doi.org/10.1159/000313828.
19. Abraham NG,Cao J, Sacerdoti D, Li X, Drummomd G. Heme oxygenase: the key to renal function regulation. Am J Physiol Renal Physiol. 2009;297:F1137-52, http://dx.doi.org/10.1152/ajprenal.90449.2008.
20. Ferrara N. The Biology of Vascular Endothelial Growth Factor. Endocr Rev. 1997;18(1):4-25, http://dx.doi.org/10.1210/er.18.1.4.
21. Basile DP, Fredrich K, Chelladurai B, Leonard EC, Parrish AR. Renal ischemia reperfusion inhibits VEGF expression and induces ADAMTS-1, a novel VEGF inhibitor. Am J Physiol Renal Physiol. 2008;294:F928-F36, http://dx.doi.org/10.1152/ajprenal.00596.2007.
22. Constantinides CA, Tyritzis SI, Evangelou C, Kyroudi A, Liatsikos E, Karamessinis P, et al. Vascular endothelial growth factor protein expression in a renal ablation rabbit model under prolonged warm and cold ischemia. Am J Nephrol. 2008;28(3):438-45.
23. Nogueira JM, Haririan A, Jacobs SC, Weir MR, Hurley HA, Al-Qudah HS, et al. The detrimental effect of poor early graft function after laparoscopic live donor nephrectomy on graft outcomes. Am J Transplant. 2009;9(2):337-47.
24. Buzdon MM, Cho E, Jacobs SC, Jarrell B, Flowers JL. Warm ischemia time does not correlate with recipient graft function in laparoscopic donor nephrectomy. Surg Endosc. 2003;17(5):746-9, http://dx.doi.org/10.1007/s00464-002-8860-4.
25. Simforoosh N, Basiri A, Shakhssalim N, Ziaee SAM, Tabibi A, Moghaddam SMMH. Effect of warm ishemia on graft outcome in laparoscopic donor nephrectomy. J Endourol. 2006;20(11):895-8, http://dx.doi.org/10.1089/end.2006.20.895.
26. Yang CC, Lin LC, Wu MS, Chien CT, Lai MK. Repetitive hypoxic preconditioning attenuates renal ischemia/reperfusion induced oxidative injury via upregulating HIF-1 alpha-dependent bcl-2 signaling. Transplantation. 2009;88(11):1251-60, http://dx.doi.org/10.1097/TP.0b013e3181bb4a07.
27. Khoury W, Jakowlev K, Fein A, Orenstein H, Nakache R, Weinbroum AA. Renal apoptosis following carbon dioxide pneumoperitoneum in a rat model. J Urology. 2008;180(4):1554-8.
28. Ollinger R, Kogler P, Biebl M, Sieb M, Sucher R, Bosmuller C, et al. Protein levels of heme oxygenase-1 during reperfusion in human kidney transplants with delayed graft function. Clin Transplant. 2008;22(4):418-23, http://dx.doi.org/10.1111/j.1399-0012.2008.00800.x.