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Laparoscopic Versus Open Bilateral Nephrectomy in Transplant Recipients With Medication-Resistant Hypertension: Final Results of a Multicenter Study With 15 Years of Follow-up

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ABSTRACT

Background. The objective of this study was to evaluate the outcomes of laparoscopic bilateral nephrectomy (LBN) compared with open bilateral nephrectomy (OBN) in transplant recipients with medication-resistant hypertension.

Material and Methods. Between 1994 and 2009, 66 renal transplant recipients underwent LBN due to poorly controlled hypertension. We compared them with 44 previous patients who underwent OBN.

Results. The mean operative times for LBN and OBN were 195.4 ± 60.1 minutes and 145.7 ± 30.2 minutes, respectively ($P = .013$). The mean hospital stays were 4.2 ± 2.1 in the LBN versus 10.3 ± 3.9 days in the OBN groups; the mean complication rates were 9.1% versus 18.2%, respectively. At follow-up, the blood pressure (mean value 130/90 mm Hg) in 45 patients (68.2%) among the LBN group was well controlled without the need for antihypertensive medications. In 19 patients (28.8%) significantly fewer antihypertensive drugs (1 or 2) were needed compared with the preoperative status. The remaining 2 patients (3%), both of whom had returned to hemodialysis due to chronic transplant rejection, remained on a combination of 3 or more antihypertensive drugs. Among the open surgery group, 23 subjects (52.3%) showed significantly decreased arterial blood pressure without needing medical therapy; 18 patients (40.9%) required 1 or 2 drugs and the remaining 3 (6.8%) were on a combination of 3 or more antihypertensives. The last cohort had returned to hemodialysis due to chronic transplant rejection.

Conclusions. LBN showed a higher efficacy than open surgery to treat medication-resistant hypertension after renal transplantation, reducing the postoperative trauma and the morbidity rate in high-risk transplant recipients.

LAPAROSCOPIC bilateral nephrectomy (LBN) has been performed for various nonmalignant indications, such as poorly controlled hypertension after renal transplantation, heavy proteinuria, and recurrent urinary tract infections associated with vesicoureteral reflux.[1] Poorly controlled hypertension remains a possible indication in selected patients because many of them have received maximal doses of multiple antihypertensive drugs. The common causes of hypertension that have to be ruled out in advance are as follows: chronic transplant rejection, native kidney disease, recurrent disease involving the renal transplant, and transplant artery stenosis.[2,3] Additionally, cyclosporine and steroids can induce or aggravate high blood pressure.[3,4] Hypertension is an important risk factor for the cardiovascular system that affects long-term renal transplant survival.[3–6] In some patients, blood pressure remains high despite antihypertensive treatment; removal of the

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native kidneys may be effective to normalize blood pressure.[7–11]

Bilateral nephrectomy can be performed via various approaches, eg, open transperitoneal operations using subcostal, flank, or midline incisions, bilateral dorsal lumbotomy, or transperitoneal laparoscopy.

In recent years, laparoscopic surgery has gained widespread acceptance among urologists. It has been applied to most urologic pathology. Today it is the gold standard in renal surgery with real benefit for the patients because it is considerably less traumatic compared with open surgery.[12] The question that must be investigated is whether laparoscopy is a safe procedure to remove both kidneys in immunosuppressed patients with poorly controlled hypertension. The null-hypothesis of this study was that, due to reduced surgical trauma and the minimally invasive nature of laparoscopic procedures, patients would obtain greater advantages with this procedure. The secondary aim was to determine whether laparoscopy was safe for transplant recipients with poorly controlled hypertension.

MATERIALS AND METHODS

Between 1994 and 2009, we performed LBN for poorly controlled hypertension on 66 renal transplant recipients at 2 hospitals (Halle and Lübeck). They included 65 cadaveric (including 2 repeat recipients) and 1 living-related donor cases. Demographic data are shown in Table 1.

Typically patients were admitted to hospital the day prior to the operation for routine diagnostic investigations. They were given a clear liquid diet with oral intake stopped 10 hours preoperatively. Intravenous antibiotics (cephalosporin or penicillin) were administered 1 hour preoperatively. Oral immunosuppressive medications provided at regular intervals on the day of the operation were continued during the hospital stay. In all cases, the indication for bilateral nephrectomy was poorly controlled hypertension (mean resting value >150/90 mm Hg), which had developed prior to transplantation. Treatment had included a salt-restricted diet and at least 3 different antihypertensive drugs. Treatable causes for hypertension were excluded using noninvasive methods. There was no case of transplant artery stenosis as assessed using magnetic resonance (MR) angiography and Doppler ultrasound techniques, the ranges of sensitivities for which are reported to be 35% to 100%. Due to the specific, considerably lower sensitivity of plasma renin levels to detect renal artery stenosis under calcineurin inhibitor treatment, we refrained from using this method.

Patients on cyclosporine and tacrolimus had stable blood levels within the therapeutic range. No patient received more than 10 mg prednisolone daily. Patients with impaired renal function underwent a transplant biopsy to exclude rejection or cyclosporine toxicity. Therefore, hypertension was assumed to be related to the native kidney. The number, type, and dosage of antihypertensive drugs were checked preoperatively and postoperatively during the hospital stay as well as during follow-up investigations.

For comparison, we selected 44 renal transplant recipients who had undergone open bilateral nephrectomy (OBN) between November 1982 and January 1994 who were matched for age, gender, body mass index, kidney size, resting blood pressure value, and number of antihypertensive drugs. Preoperative preparation was comparable to that for patients in the laparoscopy group. All complications occurring within 30 days after surgery were included in the study.

Table 1. Preoperative Data

	OBN	LBN
No. of patients	44	66
Mean age (y)	49 ± 17	45 ± 17
Body mass index	28.4 kg/m^2	27.7 kg/m^2
Ratio male/female	0.9	1.1
Immunsuppression regimen		
Triple	39/44	62/66
Triple + 1	5/44	4/66
Mean rest value of blood pressure	175/100 mm Hg	180/105 mm Hg
Mean no. of antihypertensive drugs	3	3

They were defined according to the Dindo-modification of the Clavien system,[13] as following: grade 1 (without the need for pharmacological treatment or surgical interventions); grade 2 (requiring pharmacological treatment); and grade 3 (requiring surgical interventions). No grade 4 or 5 complications were observed.

Office-based blood pressure measurements were taken in both groups using an automatic oscillometric Omron HEM-705 monitor (Omron Healthcare, Vernon Hills, Ill, United States) with a printer for documentation. Blood pressure was measured according to protocol-specified guidelines based on Standard Joint National Committee VII, European Society of Cardiology, and European Society of Hypertension recommendations.[14] We used averages of triplicate measurements for our analysis.

To assess blood pressure at home, we provided patients with an automatic Omron HEM-705 monitor to record 2 weeks of daily measurements of seated blood pressures at 3 times in the morning and 3 times in the evening. We averaged the home measurements at baseline and at each 6-month visit for our analysis.

We measured 24-hour ambulatory blood pressure with an oscillometric Spacelabs 90207 monitor (Spacelabs Healthcare, Issaqua, Wash, United States) with readings taken every 15 minutes in the daytime and every 30 minutes at night-time. We calculated overall 24-hour averages for every patient. Only ambulatory blood-pressure assessments that met European Society of Cardiology and European Society of Hypertension guidelines (with more than 70% of daytime and night-time readings) were regarded as technically sufficient for inclusion in the analysis.

The mean follow-up of 9.3 ± 7.2 years was calculated from the date of surgery to that of the most recently documented examination. No patient was lost during the follow-up. The surgical technique has been previously described[10]; all procedures were performed by 2 experienced laparoscopic and open surgeons (F.G., P.F.).

The data are presented as mean values (± standard deviations). Statistical analysis was performed using Graphpad Instat 3 (GraphPad Software Inc., Avenida de la Playa, Calif, United States). Comparisons between the groups were performed using unpaired *t* tests (Mann-Whitney, confidence interval [CI] = 95%). For all calculations, a *P*-value < .05 was considered to be significant.

RESULTS

The mean ages of patients who underwent LBN and OBN were 45 ± 17 years and 49 ± 17 years, and mean body mass index was 26.5 kg/m^2 and 27.2 kg/m^2, respectively. The corresponding mean kidney sizes were 5.3 ± 2.4 cm and 5.5 ± 2.2 cm, respectively.

The mean operative times for LBN and OBN were 195.4 ± 60.1 minutes and 145.7 ± 30.2 minutes, respectively (P = .032). The mean estimated blood loss result was 345.2 ± 275.6 mL in patients who underwent LPN versus 440.3 ± 310.2 mL in the OBN group (P = .037), with transfusion rates of 5.9% and 7.3%, respectively (P = .045).

Oral intake and mobilization were started on the first postoperative day in all patients who underwent LBN and on the third day after OBN. In 65 patients, LBN was completed successfully, using 14.2 ± 4.3 mg morphine-equivalent for postoperative pain control, whereas it was 5 times higher among the open surgery group (71.3 ± 39.6 mg; P = .012).

The mean hospital stay was 4.2 ± 2.1 versus 10.3 ± 3.9 days in the laparoscopic versus open groups (P = .025) and mean return to normal activities was 16.4 ± 4.2 versus 36.6 ± 8.3 days, respectively (P = .013).

The mean complication rate was 9.1% in the LBN and 18.2% in the OBN groups (P = .017), with a conversion rate of 1.5% in the laparoscopic group.

One LBN patient required conversion to an open procedure through an 8-cm pararectal incision between 2 trocars in the right midclavicular line due to bleeding from the vena cava, with no further complications (Clavien grade 3). This patient received 3 units of blood. Two patients displayed fever of undetermined cause with deferescence 2–5 days after priscription of oral penicillin. Urinary tract infections in 3 women were treated successfully with oral cephalosporin for 5 days (Clavien grade 2). No late complications, such as incisional herniaes, were noted; all patients were satisfied with the cosmetic result.

In the open group, 1 patient required 4 units of blood after injury to the vena cava. A surgical exploration was necessary in 2 patients due to hematomas (Clavien grade 3). One patient presented with a chest infection that resolved after 8 days of antibiotic treatment and urinary tract infections treated with ciprofloxacin occurred in 2 patients (Clavien grade 2). Two patients displayed wound complications on the 8th and 11th postoperative days, respectively, requiring a new intervention and surgical revision (Clavien grade 3). Renal transplant function remained stable in all patients who underwent LBN with no rejection or infection occurring during the hospital stay.

At follow-up, 68.2% of the LBN group showed well-controlled blood pressure without the need for antihypertensive medication: mean value 130/90 mm Hg (n = 45). In 19 patients (28.8%) significantly fewer antihypertensive drugs (1 or 2) were needed compared with the preoperative status. The remaining 2 patients (3%) both of whom had returned to hemodialysis (HD) due to chronic transplant rejection remained on a combination of 3 or more antihypertensive drugs.

Among the open surgery group, 23 patients (52.3%) showed significantly decreased arterial blood pressure without need for medical therapy whereas 18 patients (40.9%) required 1 or 2 antihypertensive drugs and the remaining 3 who had returned to HD due to chronic transplant rejection (6.8%) were still on a combination of 3 or more different antihypertensive drugs (Table 2).

DISCUSSION

Late complications of renal transplant recipients include those associated with chronic immunosuppression and arterial hypertension. Following successful renal transplantation, many patients require more antihypertensive drugs.[4] In part, these alterations are caused by chronic transplant insufficiency and immunosuppressive medications; however, often the causes of the aggravated hypertension are unknown.[10]

Hypertension, a common problem following renal transplantation, is an important cardiovascular risk factor, affecting long-term renal transplant survival.[3–6] The most frequent causes of hypertension are chronic rejection and pharmacological effects of calcineurin inhibitors. Furthermore, transplant artery stenosis and other forms of secondary arterial hypertension must be ruled out.[3,4] Poorly controlled hypertension is occasionally seen in transplant recipients; removal of both native kidneys may be an effective option to normalize their blood pressure.[3,7,9]

Twenty years ago many patients underwent OBN before planned renal transplantation. Nevertheless it was associated with high morbidity and mortality, as reported in some earlier series, with values of 3.6%–4% and 18%–40%, respectively.[6,7,10,11] Castaneda et al reported that 15/19 patients who underwent OBN for severe hypertension following renal transplantation experienced decreased blood pressure postoperatively.[8] Curtis et al reported that the mean arterial pressure and vascular resistance of the renal transplant decreased postoperatively among 6 patients who underwent OBN.[7] Since the first laparoscopic nephrectomy in 1990, this minimally invasive technique has

Table 2. Intraoperative and Postoperative Data

	OBN	LBN	P
Mean operative time (min)	145.7 ± 30.2	195.4 ± 60.1	.032
Mean estimated blood loss (mL)	440.3 ± 310.2	345.2 ± 275.6	.037
Transfusion rate (%)	7.3	5.9	.045
Complication rate (%)	18.2	9.1	.017
Mean analgesic requirement (mg)	71 ± 39	14 ± 4	.012
Mean resumption of oral intake (d)	3	1	.042
Mean kidney size (cm)	5.5 ± 2.2	5.3 ± 2.4	.123
Mean hospital stay (d)	10.3 ± 3.9	4.2 ± 2.1	.025
Mean convalescence (d)	36.6 ± 8.3	16.4 ± 4.2	.013
Successful rates (patients):			
No medical therapy	23	45	
1–2 antihypertensive drugs	18	19	
3 antihypertensive drugs	3	2	

undergone dramatic development in urology and other surgical disciplines. The minimally invasive nature of laparoscopic compared with open nephrectomy has been shown by our group due to the limited acute systemic reaction associated with laparoscopic access.[12,15] Furthermore, laparoscopic renal procedures are being used more often because of the reduced postoperative pain, shorter hospitalizations, and more rapid convalescence.[15,16]

Activation of the acute-phase response, as assessed by the level of the acute-phase C-reactive protein (CRP), correlates strongly with erythropoietin (EPO) resistance (defined by the ratio of the weekly EPO dose to hematocrit), hypoalbuminemia, and mortality in both HD and peritoneal dialysis (PD) patients.[17] Furthermore, elevated CRP levels as happens during an acute inflammatory process may increase the risk of atherosclerotic vascular disease leading to hypertension and renal failure.[18] Because laparoscopy is associated with a reduced acute-phase response and lower levels of CRP compared with open surgery, there may be a reduced risk of atherosclerotic vascular disease, explaining the better cure rates reported among LBN patients.

The first reports concerning LBN for uncontrolled hypertension appeared in the 1990s. In 1994 Bales et al reported experience with 2 patients who had well-controlled blood pressure postoperatively.[19] More recently, Sanjeevan et al noted no significant complications with simultaneous LBN in 2 patients with end-stage renal disease and severe uncontrolled hypertension.[20] In 2005 Branco et al described a 32-year-old man with end-stage renal disease who had undergone a cadaveric renal transplantation and presented with chronic transplant dysfunction and refractory hypertension. The patient underwent a LBN without complications.[21]

Our series comprised 110 patients from 2 centers (Halle and Lübeck). The criteria to perform a (laparoscopic) bilateral nephrectomy in a transplant recipient were the following[22]: (1) intractable blood pressure despite treatment with 3 or more antihypertensive drugs using maximum-tolerated doses of each, after having investigated and excluded other possible causes; (2) exclusion of stenosis of the transplant artery and other treatable causes of hypertension; (3) exclusion of chronic transplant rejection; (4) younger patients without signs of progressive general arteriosclerosis; and (5) patient permission.

The longer operative time for LBN than OBN can be explained by the initial learning curve that accompanied our first experiences. The complication rates and their severity according to the Clavien classification were reduced after LBN: 9.1% for LBN and 18.2% for OBN. In the laparoscopic group, we did not observe any wound healing problems, whereas wound complications occurred in 2 patients after OBN.

As already known, one drawback of performing surgery in transplant recipients under immunosuppression is the risk of wound infections. A laparoscopic procedure requires less skin incision, making it reasonable to expect lower rates of postoperative wound complications. Patients in the laparoscopy group benefited from rapid oral intake, decreased use of analgesics, shorter hospital stays, and earlier return to normal activities. Furthermore, oral immunosuppressive medications could be given on the day of the operation and during the entire hospital stay. This is an important point to consider because analgesic medications could decrease transplant function.

At follow-up, normalization of blood pressure was observed in 68.2% of LBN patients versus 52.3% of OBN subjects who were free of the need for medical therapy. According to these results, a selected group of renal transplant recipients may benefit in terms of a better transplant prognosis as a result of a normalized blood pressure after LBN.

In conclusion, LBN showed a greater efficacy than open surgery to treat medication-resistant hypertension after renal transplantation, reducing at the same time the postoperative trauma and the morbidity among high-risk patients, such as transplant recipients.

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