Original Article

J Korean Soc Transplant 2016;30:24-30
http://dx.doi.org/10.4285/jkstn.2016.30.1.24

JKST

Effect of Simultaneous Nephrectomy on Perioperative Blood Pressure and Graft Outcome in Renal Transplant Recipients with Autosomal Dominant Polycystic Kidney Disease

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Background: For various reasons, kidney transplant recipients with autosomal dominant polycystic kidney disease (ADPKD) often undergo native nephrectomy in preparation for the transplantation. Simultaneous nephrectomy can result in hypotensive events perioperatively and affect transplant outcome adversely. Our aim was to evaluate the effect of simultaneous native nephrectomy (SNx) on perioperative blood pressure and graft outcome compared to non-nephrectomy (NNx) in renal transplant recipients with ADPKD.

Methods: Data regarding renal function and blood pressure were collected from 42 renal transplant recipients with ADPKD. The primary outcome was graft function over 1 year post-transplant. The secondary outcomes were patient and graft survival, post-operative hypotensive events, and blood pressure control. We compared units of anti-hypertensive medication used by transplanted ADPKD patients in the SNx and NNx groups.

Results: Patients with SNx during kidney transplantation showed similar rates of patient and graft survival and renal function. Although they had significantly more hypotensive events during the perioperative period (69.2% vs. 37.5% in NNx, P=0.045), no harmful influence on renal function was observed. No difference in mean blood pressure during the 1-year post-transplant period was observed between the two groups; however, the SNx group required fewer units of anti-hypertensive medication.

Conclusions: SNx is a relatively safe procedure. Graft outcome in the SNx group was not inferior to that of the NNx group, and patients with SNx can have well-controlled blood pressure.

Key Words: Autosomal dominant polycystic kidney, Nephrectomy, Kidney transplantation
중심 단어: 상염색체 우성 다낭신, 신장절제술, 신장이식

INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is the most common genetic cause of chronic kidney disease(1). About 50% of patients in their 60s progress to end-stage renal failure, requiring renal replacement therapy, and ADPKD is a causal disease in ~2% of incident cases

Received July 31, 2015
Revised December 28, 2015
Accepted December 28, 2015

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of end-stage renal disease in Korea(2). It causes kidney enlargement and deformation, leading to destruction of the renal parenchyma, and thus, a decline in kidney function. Kidney transplantation is recognized as the optimal measure by replacing the malfunctioning kidneys.

The indications for and timing of nephrectomy in ADPKD patients remain controversial for those undergoing kidney transplantation(3-11). Today, there is a general consensus that pre-transplant native nephrectomy should be avoided whenever possible because maintaining native kidneys in ADPKD might help prevent renal osteodystrophy, anemia, uremia, fluid overload, congestive heart failure, and hyperkalemia(3). Pre-transplant native nephrectomy should only be carried out when there are clear indications, such as pain, recurrent hematuria, or infection. Recently, in the European Best Practice Group (EBPG) guidelines for kidney donor and recipient evaluation, pre-transplant nephrectomy was recommended for ADPKD patients when they had symptoms of severe, recurrent bleeding, infection, or stones. In addition, when there is not sufficient space for the transplant kidneys, EBPG suggests unilateral nephrectomy in ADPKD patients even if there are no symptoms(12). However, the removal of polycystic kidneys at the time of renal grafting is still controversial.

In some ADPKD patients, the size of the kidneys and associated symptoms provide sufficient indication for simultaneous native nephrectomy (SNx). However, there are concerns regarding perioperative complications associated with native nephrectomy, including hypotensive events(13,14). While we have experienced a few cases of poor graft outcome in nephrectomy patients who had severe hypotensive events during the perioperative period, few studies have addressed the association between SNx and hypotensive events and graft outcome in kidney transplantation in ADPKD patients.

Thus, the purpose of this study was to determine the effect of SNx on hypotensive events and graft outcome in ADPKD patients who underwent kidney transplantation. The primary outcome was graft function after kidney transplantation, with or without simultaneous nephrectomy, and the secondary outcomes were patient and graft survival, postoperative hypotensive events, and blood pressure control.

MATERIALS AND METHODS

The local ethics committee approved this study. We retrospectively reviewed the records of the 52 patients with ADPKD who underwent kidney transplantation at Seoul National University Hospital from 1999 to 2012. Ten patients were excluded from the analysis due to nephrectomy prior to kidney transplantation (n=8), inadequate data (n=1), and loss to follow-up (n=1). After transplantation, the patients had regular outpatient visits at the transplantation center. Serum creatinine was measured by the isotope dilution mass spectrometry traceable method, and estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula. Preoperative blood pressure was measured at the medical office prior to kidney transplantation. Postoperative blood pressure was recorded in an inpatient setting within the first week, after which it was measured during follow up in the medical office for 1 year, beginning 1 month after kidney transplantation. Hypotensive event was defined as a drop in systolic blood pressure greater than 40 mmHg or the need for volume resuscitation or inotropics to maintain adequate blood pressure. We reviewed the patients' clinical records for the following parameters: age at transplantation, gender, height, and weight at transplantation, date of transplantation, presence of hypertension, preoperative and postoperative blood pressure, units of antihypertensive medication, graft source, cold ischemic times, immunosuppressive therapy, time and cause of graft loss, and patient death. We calculated units of antihypertensive medication using the lowest dose in a tablet as one unit. For example, 10 mg of amlodipine corresponds to two units, as 5 mg of amlodipine is the lowest dose in a tablet.

1. Statistical analysis

Baseline numeric parameters are shown as mean±standard deviation. Fisher exact test was used to compare categorical variables. A $P<0.05$ was considered significant. Patient and graft survival were analyzed using the Kaplan-Meier method and the log-rank test. Statistical differences between units of antihypertensive medication needed due to nephrectomy were calculated using the Mann-Whitney test. The statistical analysis was performed using SPSS ver. 21.0 (IBM

Co., Armonk, NY, USA).

RESULTS

1. Demographic and transplant-related factors

Among 42 transplant recipients, 16 patients underwent kidney transplantation non-nephrectomy (NNx) group, and the other 26 patients underwent SNx group. We observed no differences between the NNx and SNx groups in regard to age (52.4±8.6 years vs. 50.2±10.4 years), prevalence of hypertension (75.0% vs. 76.9%), preoperative systolic blood pressure (137.7±17.6 mmHg vs. 131.9±14.5 mmHg), or units of antihypertensive medication (1.8±2.1 units vs. 2.3±3.4 units, all $P>0.05$). The reasons for SNx were creation of space (n=19, 70%), recurrent hematuria (n=4, 15%), recurrent infection (n=1, 5%), abdominal pain (n=1, 5%), and possibility of kidney tumor (n=1, 5%). Additional baseline clinical characteristics are listed in Table 1.

2. Perioperative clinical outcomes

The operating time of the patients in the SNx group was significantly longer than that of the NNx group (368.1±74.5 minutes vs. 240.6±76.6 minutes, $P<0.001$). In addition, estimated blood loss (719.6±432.7 mL vs. 500.0±364.9 mL) and transfusion requirements (2.8±1.7 units vs. 2.6±0.9 units) were higher in the SNx group compared to the NNx group. The only two cases of intraoperative complications, hemorrhage, and renal artery thrombosis occurred in the SNx group (Table 2).

3. Graft and patient outcome in relation to nephrectomy

One patient in the SNx group experienced graft loss and died of cyst infection-related sepsis. Another patient in the SNx group had immediate graft loss due to an intraoperative complication, renal artery thrombosis. Two other patients in the SNx group developed delayed graft function. However, we observed no significant differences in renal function outcome after nephrectomy. One year after kidney transplantation, eGFR was 60.53±13.46 mL/min/1.72 m^2 in the SNx group, compared to 66.64±11.36 mL/min/1.72 m^2 in the NNx group ($P>0.05$). The actual patient 5-year surviv-

Table 1. Baseline demographic and transplant-related characteristics

Characteristic	Non-nephrectomy (n=16)	Simultaneous nephrectomy (n=26)	*P*-value
Age (yr)	52.4±8.6	50.2±10.4	0.485
Male sex	7 (43.8)	14 (53.8)	0.525
Hypertension	12 (75.0)	20 (76.9)	>0.99
BMI (kg/m^2)	23.7±4.4	22.3±2.7	0.247
Preoperative systolic blood pressure (mmHg)	137.7±17.6	131.9±14.5	0.256
Preoperative diastolic blood pressure (mmHg)	83.6±16.3	83.7±10.7	0.975
Units of antihypertensive medication	1.8±2.1	2.3±3.4	0.968
% Use			
ACE inhibitors/ARBs	37.5	50.0	0.442
β-Blockers	31.3	15.4	0.267
Calcium channel blockers	50.0	38.5	0.475
Diuretics	6.3	15.4	0.387
Vasodilators	0	3.9	0.440
α1-Blockers	6.3	11.5	0.864
Donor relationship			
Living	6 (37.5)	9 (34.6)	0.85
Deceased	10 (62.5)	17 (65.4)	
Immunosuppressive therapy			
Tacrolimus	9 (56.3)	17 (65.4)	>0.99
Cyclosporine	5 (31.2)	9 (34.6)	

Data are presented as mean±SD or number (%).
Abbreviations: BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

Table 2. Perioperative clinical outcomes

Variable	Non-nephrectomy (n=16)	Simultaneous nephrectomy (n=26)	*P*-value
Operative time (min)	240.6±76.6	368.1±74.5	<0.001
Estimated blood loss (mL)	500.0±364.9	719.6±432.7	0.189
RBC transfusion (units)	2.6±0.9	2.8±1.7	0.807
Cold ischemic time (min)	60.8±45.3	53.5±34.5	0.569
Urinary leakage	0	0	-
Hemorrhage	0	1	-
Thrombosis	0	1	-
Wound infection	0	0	-
Urinary stricture	0	0	-
Vascular stenosis	0	0	-
Hypotensive events	6 (37.5)	18 (69.2)	0.045

Data are presented as mean±SD or number (%).
Abbreviation: RBC, red blood cell.

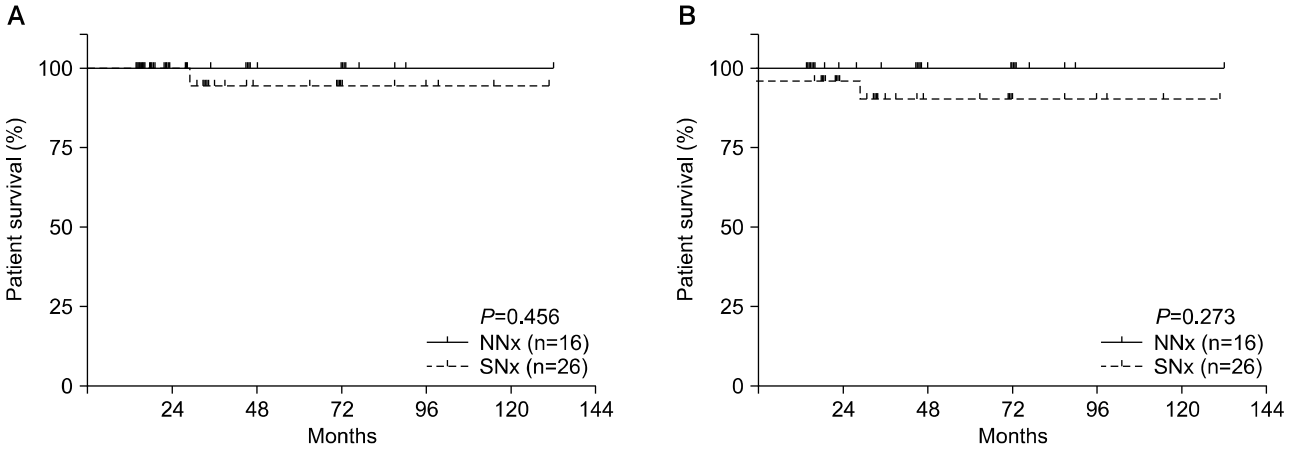


Fig. 1. Kaplan-Meier curves for (A) patient survival and (B) graft survival between non-nephrectomy (NNx, n=16) and simultaneous native nephrectomy (SNx, n=26) groups. *P*-value is estimated by log-rank test.

al rates were 100% vs. 94.4% (*P*=0.456) (Fig. 1A) and the graft survival rates were 100% vs. 90.5% (*P*=0.273) in the NNx and SNx groups, respectively (Fig. 1B).

4. Perioperative blood pressure and its effect on graft outcome

There were more hypotensive events in the SNx group (n=18, 69.2%) than in the NNx group (n=6, 37.5%, *P*=0.045). We explored the effects of native nephrectomy on blood pressure and graft outcome in terms of hypotensive events. All of the subjects in the SNx group were subdivided into two groups according to hypotensive events. There were no significant differences in demographic or transplant-related characteristics between the two groups (Table 3). We analyzed renal function outcomes related to hypotensive events. One patient in the SNx group who experienced a hypotensive event was excluded from the renal function outcome analysis because there was immediate graft loss due to renal artery thrombosis. One year after kidney transplantation, although not significant, the hypotensive events group had higher eGFRs than the non-hypotensive events group did (64.04±12.61 mL/min/1.73 m^2 vs. 53.09±12.82 mL/min/1.73 m^2, *P*=0.056) (Supplementary Table 1 Online).

There was no difference in systolic blood pressure between the NNx and SNX groups during the 1-year follow-up (Fig. 2A). We examined the number of units of antihypertensive medication needed due to nephrectomy.

Table 3. Demographic and transplant-related characteristics related to hypotensive events in the simultaneous native nephrectomy group

Variable	Hypotensive events (n=18)	Non-hypotensive events (n=8)	*P*-value
Age (yr)	49.33±10.28	52.13±11.15	0.539
Male sex	9 (50)	5 (62.5)	0.683
Hypertension	12 (67)	8 (100)	0.132
BMI (kg/m^2)	21.72±2.70	23.44±2.33	0.144
Preoperative systolic blood pressure (mmHg)	129.50±14.75	137.25±13.08	0.214
Preoperative diastolic blood pressure (mmHg)	83.44±9.90	84.38±13.01	0.842
Units of antihypertensive medication	2.1±2.1	2.1±3.5	0.350
% Use			
ACE inhibitors/ARBs	38.7	75.0	0.096
β-Blockers	16.7	12.5	0.796
Calcium channel blockers	33.3	50.0	0.440
Diuretics	11.1	25.0	0.385
Vasodilators	5.6	0	0.516
α1-Blockers	11.1	0	0.163
Patients on >3 antihypertensive medications	4 (22.0)	2 (25.0)	0.883
Donor relationship			
Living	5 (27.7)	4 (50)	0.382
Deceased	13 (72.2)	4 (50)	
Immunosuppressive therapy			
Tacrolimus	11 (61.1)	6 (75)	0.667
Cyclosporine	7 (38.8)	2 (25)	

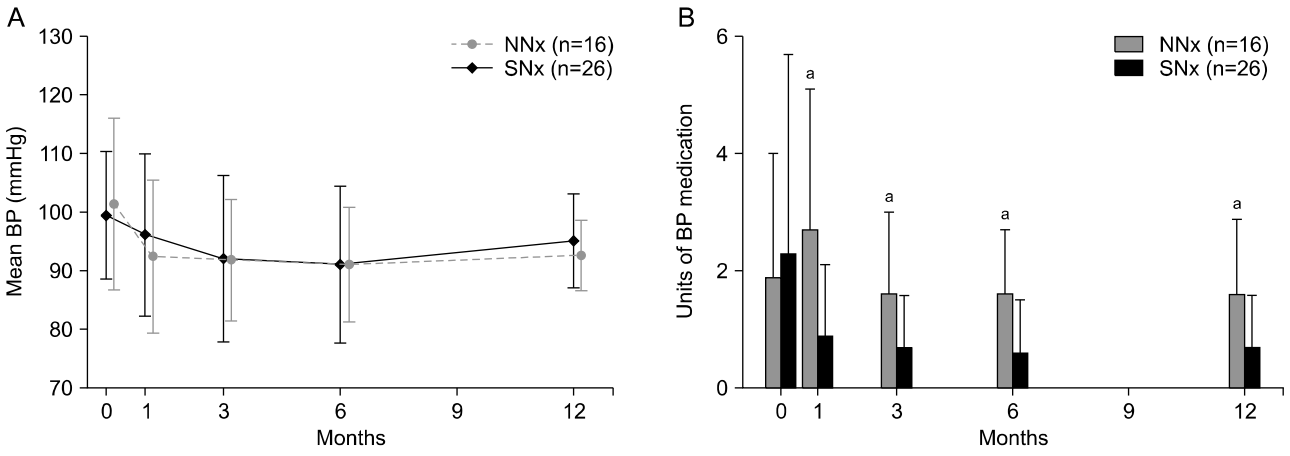
Data are presented as mean±SD or number (%).
Abbreviations: BMI, body mass index; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker.

While there were no significant differences in the preoperative period, fewer units of antihypertensive medication were used in the SNx group than in the NNx group at 1 month (0.9±1.2 vs. 2.7±2.4, *P*=0.003), 3 months (0.7±0.9 vs. 1.6±1.4, *P*=0.013), 6 months (0.6±0.9 vs. 1.6±1.1, *P*=0.002), and 12 months (0.7±0.9 vs. 1.6±1.3, *P*=0.016), respectively (Fig. 2B).

DISCUSSION

This retrospective, single-center study sought to evaluate the effects of SNx on graft outcome and blood pressure in ADPKD patients who underwent kidney transplantation. Regarding indications and timing of native nephrectomy, in the 1970s, bilateral nephrectomy prior to transplantation was a common procedure. The risk of infectious complications in patients who underwent nephrectomy prior to transplantation was reduced; however, it was at the cost of increased perioperative risk, loss of diuresis, diminished quality of life, or progression of anemia. While it is now believed that pre-transplant nephrectomy should not be routine and has no advantage over transplantation with both native kidneys intact(15), native nephrectomy is still recommended in patients with refractory symptoms. Severe hypotensive events, which were probably associated with native nephrectomy, prompted us to investigate the relationship between hypotensive events after kidney transplantation and renal function outcomes.

In this study, SNx did not result in the adverse effects on graft outcome or patient survival that were reported in previous studies(5,6,8). However, hypotensive events during the immediate postoperative period occurred more often with native nephrectomy. Hypertension develops early in the life of ADPKD patients. Increased activity of the renin-angiotensin system (RAS) associated with extracellular volume expansion might play an important role in the development of hypertension in these patients(16,17). It has been suggested that cyst expansion, leading to focal areas of renal ischemia and enhanced renin release, is responsible for high blood pressure. Thus, native nephrectomy might



Systolic blood pressure during follow-up period according to nephrectomy

Time	Non-nephrectomy	Simultaneous nephrectomy
Pre-operative	137.7±17.6 (15)	131.9±14.5 (26)
1 month	124.6±15.5 (7)	128.1±14.5 (9)
3 months	123.9±13.0 (9)	122.6±18.2 (19)
6 months	121.0±13.0 (9)	120.9±18.2 (19)
12 months	123.5±7.7 (8)	128.8±14.0 (18)

Units of anti-hypertensive medication according to nephrectomy

Time	Non-nephrectomy	Simultaneous nephrectomy
Pre-operative	1.9±2.1	2.3±3.4
1 month	2.7±2.4	0.9±1.2
3 months	0.6±1.4	0.7±0.9
6 months	1.6±1.1	0.6±0.9
12 months	1.6±1.3	0.7±0.9

Fig. 2. (A) Mean blood pressure (BP; mmHg, mean±SD [total no.]) and (B) units of antihypertensive medication during follow-up period after nephrectomy. Abbreviations: NNx, non-nephrectomy; SNx, simultaneous native nephrectomy. [a]$P<0.05$.

eliminate the source of renin-angiotensin release, resulting in a favorable effect on blood pressure control, as well as relieving the mass effect of cystic kidneys. In this study, patients with native nephrectomy had more hypotensive events, but they were reduced with antihypertensive medications during the follow-up period. In turn, the hypotensive event group had comparable renal function. Overall, the ADPKD patients with native nephrectomy showed similar graft function and blood pressure level results with fewer antihypertensive medications, possibly due to diminished RAS activation. The favorable effect of native nephrectomy on blood pressure might help preserve graft function and decrease the risk of cardiovascular morbidity in ADPKD patients.

While patients who have undergone nephrectomy tend to have longer operating times, there were no significant differences in terms of perioperative complications in this study. One patient in our study had immediate graft loss due to renal artery thrombosis, which was not related to the nephrectomy. Enlarged kidneys in ADPKD often cause adhesion to peritoneum or adjacent organs, resulting in wide dissection in nephrectomy procedures and intraoperative bleeding. Mean estimated blood loss in SNx group was 1.4-fold higher than NNx group; however, there was no significant difference in this study. In addition, cold ischemic time in SNx group was not longer than that in NNx group, which may be explained by the fact that the time between native nephrectomy and the donor kidney implantation was controlled in Seoul National University Hospital.

CONCLUSION

In conclusion, SNx is a relatively safe procedure, and in this study, graft outcome in patients who underwent SNx was not inferior to that of patients who did not undergo SNx. Although SNx could have a potential risk of hypotensive events, with the support of careful monitoring and intervention, it had no harmful influence on outcome.

However, this study had several limitations. The small sample size probably limited statistical power to report a significant difference, and the reason the hypotensive events group had good renal function was not fully investigated. Prospective studies to measure renin-angiotensin level and evaluate cardiac function will be needed in the future.

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Supplementary Table 1. Renal function outcomes related to hypotensive events in recipients with simultaneous nephrectomy

	Non-hypotensive events (n=8)	Hypotensive events (n=17)	*P*-value
Pre-operative eGFR	7.16±2.76	8.24±3.13	0.414
Post-operative 1 month eGFR	53.10±13.42	61.33±12.36	0.144
3 months eGFR	49.75±10.92	58.94±11.88	0.078
6 months eGFR	50.04±13.02	60.92±10.63	0.036
12 months eGFR	53.09±12.82	64.04±12.61	0.056

Data are presented as mean±SD.
Abbreviation: eGFR, estimated glomerular filtration rate.