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Observational Study

Simultaneous nephrectomy during kidney transplantation for polycystose does not detrimentally impact comorbidity and graft survival

Darius T *et al.* Simultaneous ipsilateral nephrectomy during kidney transplantation for ADPKD.

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Abstract

BACKGROUND

The lack of space, as indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other Autosomal Dominant Polycystic Kidney Disease-related symptoms, remains controversial.

AIM

³ The aim of this study was to evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease.

METHODS

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

RESULTS

Creation of space for future graft positioning was the main reason ($n = 74$, 96.1%) for associated ipsilateral nephrectomy. No significant difference in surgical comorbidity (lymphocoele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed between both study groups. The incidence of primary nonfunction and delayed graft function was comparable in both groups (0% and 2.6% ($P = 0.497$) and 9.1% and 16.9% ($P = 0.230$), respectively in the KTA and KTIN group). The 1 and 5-year graft survival were 94.8% and 90.3 and 100% and 93.8%, respectively in the KTA and KTIN group ⁴ ($P = 0.774$). The 1 and 5-year patient survival were 96.1% and 92.9% and 100% and 100%, respectively in the KTA and KTIN group ($P = 0.168$).

CONCLUSION

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease does not negatively impact surgical comorbidity and short and long-term graft survival.

Key Words: Autosomal dominant polycystic kidney disease; complications; kidney transplantation; graft survival; unilateral nephrectomy; surgical comorbidity

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Core Tip: The associated comorbidity on surgical comorbidity and graft survival of an ipsilateral nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease was evaluated. 154 patients were retrospectively evaluated, of which 77 without and 77 with associated ipsilateral nephrectomy during the transplantation. In a long-term follow-up we observed no negative impact on surgical comorbidity and graft survival of a simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease.

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INTRODUCTION

Autosomal dominant polycystic kidney disease (ADPKD) is one of the most frequent causes of renal failure in Europe and USA and may affect 2.5% to 10% of the dialysis patients. Renal failure is the result of the development and progressive expansion of multiple bilateral cysts in the renal parenchyma, leading to a progressive decline in renal function owing to compression of normal functioning parenchyma by enlarging cysts.(1-3)

Clear indications for nephrectomy before transplantation include invalidating pain and discomfort, ongoing hematuria, recurrent severe cysts infections, gastrointestinal symptoms such as early satiety, recurrent nephrolithiasis and risk of malignancy.(1, 2, 4) Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of an increased surgical co-morbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation. However, many controversies still exist concerning the indication and timing of an unilateral nephrectomy to create space for graft positioning in an asymptomatic kidney transplant candidate suffering from massive enlarged polycystic kidney.(3, 5, 6)

Therefore, the aim of this retrospective study was to evaluate the surgical comorbidity and the impact on early and late graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in ADPKD patients. Based on these results a symptom-based algorithm is proposed to decide the timing and necessity of a unilateral or bilateral nephrectomy in ADPKD candidates waiting for, or during transplantation.

MATERIALS AND METHODS

Donor and recipient demographics

Figure 1 illustrates the selection flowchart of this retrospective study. Between January 1, 2007 and January 1, 2019, a total of 1026 kidney transplantations were performed at the University Clinics Saint-Luc (Brussels, Belgium) of which 154 patients underwent isolated kidney transplantation for ADPKD. This selection was obtained using the following inclusion criteria: isolated kidney transplant recipient, ADPKD as primary cause of renal failure, age above 18 years old. The exclusion criteria were the following: multi-organ recipients, ADPKD not as primary kidney disease and paediatric recipients. No patients were lost from follow-up. From these 154 ADPKD patients, 77 underwent a

kidney transplantation alone (KTA group) and 77 a kidney transplantation with associated native ipsilateral nephrectomy (KTIN group) and were retrospectively reviewed. This study was approved by the institutional ethical committee. The following donor characteristics were analyzed: age, gender, type of donor (living *vs* deceased) and type of deceased donor (donation after brain death or donation after circulatory death) and cytomegalovirus status. Recipient characteristics included: age, gender, body mass index (BMI), rank of transplant, time on dialysis and residual diuresis before transplantation, Human Leucocyte Antigen (HLA) mismatching, haemoglobin and albumin level before transplantation. Donor and recipient characteristics are presented in Table 1. Combined organ transplantation and ABO incompatible transplantations were excluded.

Surgical technique

A standard kidney transplant procedure was performed by a hockey stick incision with a classical vascular reconstruction on the iliac vessels and an ureterovesical anastomosis achieved according to the extravesical approach described by Lich-Gregoir.(7-9) A ureter stent was not routinely used but only according to the surgeon's preference and indication. An associated native ipsilateral nephrectomy was performed, if indicated, before implantation of the kidney graft with cranial extension up to the costal margin of the hockey stick incision by a retroperitoneal approach. Peroperative drainage of multiple renal cysts was frequently performed to facilitate surgical resection. The following surgical characteristics were collected: indications for associated ipsilateral native nephrectomy, total surgical time, anastomosis time (defined as the time from start vascular anastomosis to reperfusion of the kidney), cold ischemia time (defined as the time from start in situ cold perfusion of the kidney in the deceased donor or *ex vivo* cold perfusion of the kidney in a living donor to start in situ vascular anastomosis in the recipient) and weight of the removed native polycystic kidney.

Posttransplant immunosuppression

A triple-drug protocol consisting of tacrolimus (Advagraf, Astellas Pharma BV, Brussels, Belgium), methylprednisolone (Medrol, Pfizer NV, Brussels, Belgium) and mycophenolate mofetil (Cellcept, 2x500 mg/d, NV Roche SA, Brussels, Belgium) was used during the whole study period in all except one patient. Induction therapy with basiliximab (Simulect, Novartis Pharma GmbH, Neurenberg, Germany) on day 0 and 4 and thymoglobuline 1.25 mg/kg (Thymoglobulin, Sanofi Genzyme Europe B.V., Amsterdam, The Netherlands) day 1 until day 4 after transplantation was used in recipients of a living donor graft and a donor after circulatory death, respectively. Plasmapheresis was applied in highly immunized recipients until one month after transplantation. Tacrolimus trough levels (T_0) were between 10 and 14 ng/mL, 7 and 10 ng/mL and 5 and 7 ng/mL, during the first month, between the second and third month and from 3 mo after transplantation, respectively. Methylprednisolone was started immediately after transplant at 16 mg per day and tapered (minus 4mg every 2 wk) to a fixed dose of 4 mg for all recipients at long-term. Co-trimoxazole prophylaxis was given in all patients during the first 6 mo after transplantation. Valganciclovir prophylaxis (900 mg/day for normal kidney function) was given to all patients during the first 6 mo after transplantation at the exception of cytomegalovirus donor seronegative/recipient seronegative patients. Biopsy proven acute cellular rejection and humoral rejections were treated with methylprednisolone boluses for 3 days and plasmapheresis, respectively.

Follow-up

During the transplant hospitalization, the patients were daily followed to evaluate comorbidity and kidney function was evaluated by serum creatinine and urine analysis. If PNF, DGF or vascular problems of the kidney graft were suspect an urgent ultrasound was performed. Otherwise, a baseline ultrasound was performed at the end of the transplant hospitalization. Ambulatory follow-up of the kidney graft function (measured by serum creatinine and urine analysis) and surgical comorbidity was performed according to local center practice. No protocol, only indication biopsies of

the kidney graft were performed after preceding ultrasound. Every year after transplantation, an ultrasound of the kidney graft and the native kidneys was performed. If suspicion for malignancy of the native kidneys, a nuclear magnetic resonance was realized.

Endpoints

The primary endpoint was surgical comorbidity, measured as incidence of postoperative lymphocoele, wound infection, incisional hernia, wound hematoma, urinary infection, need for peritransplant (during and after transplantation) blood transfusion, pulmonary embolism, total hospital stay, readmission rate and surgical complications classified according to the Dindo Clavien classification.(10) Secondary endpoints were the incidence of primary nonfunction, delayed graft function (defined as the need for dialysis during the first week after transplantation), venous or arterial kidney graft thrombosis, acute rejection incidence and type of rejection (cellular *vs* humoral) during the first year after transplantation and the 1 and 5-year patient- and graft survival rate.

Statistical methods

Characteristics of the donor, the recipient and the transplant outcome were compared using the chi-square test for categorical variables and the t-test for continuous variables. Continuous variables were provided as means and standard deviations. Log-rank statistics were used with the Kaplan-Meier product-limit method to evaluate the associations of individual covariates with allograft survival. $P < 0.05$ was considered significant. Statistical analysis and plots were accomplished with SPSS 24.0 statistical software (SPSS, Chicago, IL) and Prism 8.2.0 (Graphpad Software, San Diego, CA).

RESULTS

Donor and recipient characteristics

Donor and recipient characteristics of both study groups were comparable, except the incidence of living donation, which was significantly higher in the KTIN group compared with the KTA group (21 (27.3%) vs 6 (7.8%), $P = 0.003$)(Table 1). Peritransplant plasmapheresis was performed in 14 (18%) and 3 (4%) immunized recipients in the KTA and the KTIN group, respectively ($P = 0.008$).

Operative data

The main indications to perform an associated ipsilateral native nephrectomy at the site same of the kidney transplantation were lack of space for graft positioning ($n = 74$; 96.1%), pain ($n = 29$; 37.7%) and hematuria ($n = 30$; 39.0%). Pain, as only reason for ipsilateral nephrectomy was present in 3 (3.9%) patients. The decision not to perform an associated ipsilateral native nephrectomy was taken by the surgeon during the transplant procedure if estimated enough space for graft positioning in combination with the absence of other ADPKD-related symptoms at the moment of transplantation. No difference in anastomosis and cold ischemia time was observed between both study groups (Table 2). The total surgical time was significantly longer in the KTIN group as compared with the KTA group (223.29 ± 71.96 versus 169.07 ± 44.31 , respectively; $P = 0.005$). The mean weight of the removed polycystic kidney was 2073.94 ± 1197.89 g.

Comorbidity after transplantation

No significant difference in surgical comorbidity (lymphocoele, wound infection, incisional hernia, wound hematoma, pulmonary embolism, urinary infection, need for peritransplant blood transfusion, hospitalization stay, readmission rate and Dindo Clavien classification) was observed between both study groups (Table 3).

Graft function and patient survival

The incidence of primary nonfunction and delayed graft function was comparable in both groups (0% vs 2.6% ($P = 0.497$) and 9.1% vs 16.9% ($P = 0.230$), respectively in the KTA and KTIN group)(see also Table 3). No significant difference in renal artery and

vein thrombosis of the kidney graft was observed between both study groups. And also the incidence of acute rejection within one year after transplantation was comparable among the groups.

The 1 and 5-year graft survival were 94.8% and 90.3 and 100% and 93.8%, respectively in the KTA and KTIN group ($P = 0.774$)(Figure 2). The 1 and 5-year patient survival were 96.1% and 92.9% and 100% and 100%, respectively in the KTA and KTIN group ($P = 0.168$)(see also Figure 2).

DISCUSSION

This retrospective single center study is one of the largest series that demonstrates the absence of negative impact on surgical comorbidity and short- and long-term kidney graft function of an associated ipsilateral native nephrectomy to create place for graft positioning during isolated kidney transplantation in ADPKD patients compared with ADPKD kidney transplant recipients without simultaneous nephrectomy.

The lifetime nephrectomy rate of at least one kidney is approximately 20-30% for patients with ADPKD.(11, 12) Maintaining native kidneys in ADPKD transplant candidates may help to prevent renal osteodystrophy, anemia, uremia, fluid overload, congestive heart failure, and hyperkalemia.(4, 13, 14) The advantage of maintaining total native urine output is important for dialysis comfort in patients on the waiting list for transplantation and confers some survival benefits on the waiting list.(15) Even today, the indications and timing for a native unilateral or bilateral nephrectomy in ADPKD candidates for isolated kidney transplantation remain controversial and are quite often center-dependent and based on historical routine and experience. Clear indications for unilateral or bilateral native nephrectomy before transplantation are: 1) invalidating pain and discomfort, 2) ongoing hematuria, 3) recurrent renal cysts infections and gastrointestinal pressure symptoms (e.g. early satiety), 4) recurrent nephrolithiasis (rare), 5) the suspicion of malignancy in those with complex cysts and 6) combined liver and kidney transplantation. In the absence of these clear indications, the lack of space for positioning a future kidney graft remains controversial as indication to

perform a unilateral native nephrectomy before transplantation. We agree that a simultaneous ipsilateral nephrectomy to create space during isolated kidney transplantation can be technically challenging, even in the hands of an experienced surgeon. A review of the literature, as illustrated in Table 4, does not demonstrate a significant negative impact of an associated ipsilateral or bilateral nephrectomy during isolated kidney transplantation on surgical comorbidity and early and late allograft and patient survival.(16-20) The advantage of performing the nephrectomy simultaneous with the transplantation is the avoidance of an extra anesthetic/surgical procedure and a possible status of oliguria when performed before transplantation during the time on the waiting list. In line with these previous studies, the risk of losing a kidney graft, in relation to native nephrectomy is extremely low.

The proposed algorithm to decide the optimal timing of a native nephrectomy in candidates for isolated kidney transplantation is mainly based on ADPKD-related symptoms (Figure 3). In general, we do not perform a native nephrectomy to create space for graft positioning in the absence of ADPKD-related symptoms before transplantation but by preference during the transplantation. Patients with a pretransplant clinical examination palpating a polycystic kidney below the level of the umbilicus or a radiological image showing a polycystic kidney extending into the iliac fossa, are very likely to need a ipsilateral native nephrectomy during transplant. Our center policy is to add peritransplant plasmapheresis to the standard immunosuppressive therapy in all high-immunized patients. Therefore, only for high-immunized patients with an expected long waiting time on the transplant list and high associated medical comorbidity, we consider a unilateral nephrectomy to create space for future kidney graft positioning before transplantation with the aim to decrease the risk of plasmapheresis-related surgical complications (bleeding, incisional hernias, blood transfusions, ...) during transplantation. This might explain the difference in numbers of patients receiving peritransplant plasmapheresis in favor of the KTA group in our study. For high-immunized patients with low associated medical comorbidity, our preference is to perform the associated nephrectomy during the transplantation.

Also our strategy is to avoid an unnecessary nephrectomy after transplantation. Today, it's unusual for ADPKD-patients to require nephrectomies for complications related to their native kidney (<20%) after their transplantation.(5) A nuclear magnetic resonance of the abdomen is routinely performed after transplantation to screen for malignancies in the native polycystic kidney(s). Conflicting data exists about the risk of renal cell carcinomas in ADPKD-affected kidneys. While case studies reports the occurrence of renal cell carcinomas in ADPKD-affected kidneys,(21, 22) these tumors may be partly due to acquired renal cystic disease resulting from long-term dialysis.(23) In contrast, data from the Scientific Registry of Transplant Recipients observed even a lower cancer risk in polycystic kidney disease recipients. This might be explained by the ADPKD mutations causing clearly cyst formation, but it is also possible that these mutations trigger protective cellular mechanisms that prevent cells from undergoing malignant transformation.(24) Ward CJ *et al* demonstrated that germline mutations in polycystic kidney and hepatic disease 1 were protective against colorectal cancer.(25) However, the observed lower risk of renal cancer in the Scientific Registry of Transplant Recipients can also be explained by the higher incidence of nephrectomies in ADPKD recipients in contrast with their non-ADPKD counterparts.(24)

We recognize some limitations in the present study. First, it's retrospective character. Second, in recipients with associated nephrectomy during isolated kidney transplantation, the lower incidence of peritransplant plasmapheresis and higher incidence of living donors could have underestimated the surgical comorbidity in this study group.

CONCLUSION

In conclusion, simultaneous native ipsilateral nephrectomy to create space for graft positioning during kidney transplantation in ADPKD patients does not detrimentally impact surgical comorbidity and short and long-term graft survival.

ARTICLE HIGHLIGHTS

Research background

The lack of space, as indication for a native unilateral nephrectomy for positioning a future kidney graft in the absence of other Autosomal Dominant Polycystic Kidney Disease-related symptoms, remains controversial.

Research motivation

Unilateral native nephrectomy to create space for graft positioning in an otherwise asymptomatic ADPKD patient is quite often routinely performed in isolated kidney transplant candidates before their activation on the waiting list. This strategy is mainly driven by the fear of an increased surgical co-morbidity and the possible negative impact of prolonged cold ischemia time and short- and long-term graft survival related to the associated nephrectomy during transplantation.

Research objectives

³ The aim of this study was to evaluate the surgical comorbidity and the impact on graft survival of an associated ipsilateral native nephrectomy during isolated kidney transplantation in patients with autosomal dominant polycystic kidney disease.

Research methods

One hundred and fifty-four kidney transplantations performed between January 2007 and January 2019 of which 77 without (kidney transplant alone (KTA) group) and 77 with associated ipsilateral nephrectomy (KTIN group), ⁴ were retrospectively reviewed. Demographics and surgical variables were analyzed and their respective impact on surgical comorbidity and graft survival.

Research results

No significant difference in surgical comorbidity (lymphocoele, wound infection, incisional hernia, wound hematoma, urinary infection, need for blood transfusion, hospitalization stay, Dindo Clavien classification and readmission rate) was observed

between both study groups. The 1 and 5-year graft survival were 94.8% and 90.3 and 100% and 93.8%, respectively in the KTA and KTIN group ($P = 0.774$). The 1 and 5-year patient survival were 96.1% and 92.9% and 100% and 100%, respectively in the KTA and KTIN group ($P = 0.168$).

Research conclusions

Simultaneous ipsilateral native nephrectomy to create space for graft positioning during kidney transplantation in patients with autosomal dominant polycystic kidney disease does not negatively impact surgical comorbidity and short and long-term graft survival.

Research perspectives

More kidney transplant candidates suffering from autosomal dominant polycystic kidney disease when activated on the waiting list should be proposed for an associated ipsilateral nephrectomy during the transplantation instead of routinely programmed pretransplant nephrectomy.

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