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Original article

Living donor kidney transplantation in the hemodialysis-naive and the hemodialysis-exposed: A short term prospective comparative study☆

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Abstract
Introduction: Preemptive (P) living donor kidney transplantation (LDKT) provides better survival rates, quality of life and economic saving. However, the extent of these advantages over those with a short period of pre-LDKT dialysis is not known.
Objectives: Evaluation of the patients' characteristics and short-term outcomes of PLDKT and LDKT after a pre-transplant period of hemodialysis (HD) not >6 months.
Patient and methods: This study was conducted between June 2010 and June 2012 and included two groups. Group-I included recipients without HD before operation. Group-II included those who had a period of HD ≤6 months. Recipients and donors were evaluated according to the classic work up.
Follow-up for 12 months was scheduled.
Results: Group-I included 30 recipients and group-II included 15 recipients. Demographic and clinical characteristics were similar except for mean recipient age (44 *versus* 34.3 years; $p = 0.024$), recipient donor age difference ($p = 0.03$), job categories ($p = 0.047$) and ABO distribution ($p = 0.01$). Cumulative graft (0.88 *versus* 0.93) and recipient (0.92 *versus* 0.100) survival rates were non-significantly different. Graft function and mean serum creatinine level were within normal up to 12 months. Acute graft rejection (AGR) was significantly higher in group-II (16.7% *versus* 46.7%; $p = 0.03$). However, lymphoceles were significantly

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more common in group-I (40% *versus* 6.7%; $p = 0.02$). There was no delayed graft function (DGF), major urinary or vascular complications.
Conclusion: PLDKT has a lower rate of AGR. Despite it has a higher rate of lymphoceles, it saves the patient the morbidities of vascular access and inconveniences of HD. Hence, PLDKT is recommended as the first choice for each KT-candidate.

Introduction

Kidney transplantation (KT) is the best treatment for end-stage renal disease (ESRD). It improves survival and quality of life and reduces complications [1]. This is maximized when preemptive KT (PKT) (before starting chronic dialysis) and living kidney donation (LKD) are employed [2]. Preemptive living donor kidney transplantation (PLDKT) also avoids the vascular access placement and inconveniences of dialysis. Advantages of PLDKT were documented since late 1990s [2,3]. It provides a 52% reduction of the risk of graft failure in the first year, 82% in the second and 86% during subsequent years, when compared with KT after dialysis [2]. Also, it was associated with significantly lower incidence of delayed graft function (DGF) and acute graft rejection (AGR) [4,5]. However, other post-KT complications were not studied specifically after PLDK [6].

Although the duration of dialysis before KT was reported as the strongest risk factor for graft and patient survival, the exact time-point at which this significance emerges was not well-settled [7]. Some researchers found that significant graft failure and patient mortality starts when the duration of pre-KT dialysis is >180 days and >1 year, respectively [8].

In this study, we compared the characteristics of patients and short-term outcomes including survival rates and common complications in PLDKT and living donor kidney transplantation (LDKT) after a period of dialysis ≤6 months.

Patients and methods

Between June 2010 and June 2012, 45 ESRD patients who were followed up in our department or referred to our hospital for KT were included in this prospective comparative study. They were divided into two groups according to the state of HD: KT before dialysis (PLDKT; Group-I, no: 30) or KT after a period of HD ≤6 months [Conventional LDKT (CLDKT); Group-II, no: 15]. The demographic and clinical characteristics of both groups and their short-term (1-year) outcomes were compared (Table 1). All recipients and donors were prepared routinely. HD was done for 10 patients in group-I (one and only session) and all group-II patients on the day before the operation. Medico-legally, in both groups, only the donors of 21–50 years age were accepted.

All grafts were harvested from living donors (LDs) through a classic flank incision and transplanted through a right paramedian incision to the recipients' external iliac vessels in an end-to-side fashion. Modified Lich-Gregoir technique on JJ stent was employed. The procedures were done by the same set of surgeons in all cases.

Strict post-operative measuring of serum creatinine, urine output, drain output, and fluid replacement was done up to discharge. Drain was removed on the 4th day or when its output is <100 ml/24 h. JJ-stent was removed after 4–6 weeks. Ultrasonography was used to detect any peri-graft fluid collection. Cases of AGR were managed by intravenous steroid bolus injection and if failed, by anti-thymocyte globulin.

Follow up period was 12 months.

Results

Demographic characteristics

Demographic characteristics are demonstrated in Table 1. There was no statistically significant difference between both groups regarding diabetes mellitus, hypertension, smoking, previous surgery, the main primary kidney diseases [mainly glomerulonephritis (40%), hypertensive nephropathy and polycystic kidney disease (PCKD)], degrees of HLA matching and the donated kidney parameters [total donor glomerular filtration rate (GFR), split GFR and laterality of the donated kidney].

In group-I, means of pre-KT serum creatinine and estimated GFR (eGFR) were 7.96 ± 2.0 mg/dl and 8.27 ± 4.42 ml/min/1.73 m^2, respectively.

In group-I, 23 recipients completed the 12 months follow-up, 2 recipients died and 5 were missed during follow-up. Group II included only 15 recipients who presented to us during the period of the study and fulfilled the inclusion criteria (HD for ≤6 months), all of them completed the follow up period.

Graft function and survival rates

Grafts' responses and complications during the first post-KT year are demonstrated in Table 2.

Serum creatinine levels progress

Mean serum creatinine at 1, 3, 6, 9 and 12 months remained within normal values in both groups. In group-I mean serum creatinine rose steeply but insignificantly compared to 1st month ($p = 0.07$). In group-II, mean serum creatinine remained similar or even lower than its level at 1st month ($p = 0.36$). Comparing both groups at these different time points, mean serum creatinine was comparable except at 1 month where it was significantly lower in group-I ($p = 0.049$).

In group-I, three males had mild impaired serum creatinine level in the first post-KT year and one female had marked serum creatinine

Table 1 Recipient's demographic characteristics.

Parameters	Group-I ($n=30$)	Group-II ($n=15$)	p-value
Recipient gender (M/F)%	66.7/33.3	60/40	0.66
Recipient age mean ± SD	44.1 ± 12.1	34.3 ± 14.6	0.024
Education level (%)			
High	56.7	33.3	0.35
Medium	26.7	53.3	
Low	10	6.7	
Non	6.7	6.7	
Job Category (%)			
Governmental job	40	26.7	0.047
Private work	40	13.3	
Student	6.7	33.3	
Housewife	13.3	26.7	
Body mass index mean ± SD	26.6 ± 3.5	27.4 ± 4.3	0.36
Consanguinity (R/Un-R) %	6.7/93.3	0/100	0.30
Donor gender (M/F)%	96.7/3.3	100/0	0.48
Donor age mean ± SD	30 ± 6.8	28 ± 6.3	0.47
Recipient-donor age difference (%)			
Recipient older than donor	93.3	60	0.03
Donor older than recipient	6.7	40	

M/F: Male/Female; S/M, R/Un-R: Related/Un-Related; %: percentage; SD: standard deviation.

elevation at 6 months. Impaired serum creatinine was detected in 2/29 recipients (6.8%) and in 4/23 recipients (17.4%) available for follow-up at 6 and 9 months respectively, while it was detected only in 2 recipients (8.7%) at 12-months. In group-II, highest incidence of impaired serum creatinine was detected in 3 males (20%) at 1 month post-KT. It was mild in 2 and marked in 1 recipient. After the first 3 months, only 1 (6.7%) recipient continued with impaired serum creatinine level up to 12 months.

Although it did not reach a statistical significance in the first post-KT week, the incidence of AGR was significantly lower in group-I through the first post-KT year ($p=0.03$) (Table 2).

Table 2 Early and delayed post-operative responses and complications.

Parameter	Description: percentage (%)		p value
	Group-I	Group-II	
First week responses and complications			
Start of graft function (%)			
Immediate or early graft function/DGF	100/0	100/0	
Intra-operative complications (%)			0.5
Delayed recovery from anesthesia	3.3	6.7	
Renal artery spasm	10	6.7	
Hemorrhage	–	6.7	
Days to discharge (mean ± SD)	7.3 ± 1.15	7.3 ± 1.58	1.0
Days to catheter removal(mean ± SD)	7.43 ± 1.74	7.27 ± 1.38	0.75
Days to drain removal(mean ± SD)	5.5 ± 2.9	4.47 ± 1.1	0.19
Abnormal rising serum creatinine (acute rejection; %)	10	33.3	0.054
First day of normal serum creatinine (mean ± SD)	3.86 ± 5.20	3.36 ± 2.37	0.73
Lowest serum creatinine level during 1st week (mean ± SD)	0.93 ± 0.34	1.05 ± 0.40	0.28
serum creatinine on discharge (mean ± SD)	1.07 ± 0.63	1.09 ± 0.42	0.9
Complications through the first 12-months			
Acute graft rejection including 1st week	16.7	46.7	0.03
Surgical complications			
Urinary complications:			
Pyuria (microscopic)	36.7	73.3	0.02
Hematuria (microscopic)	40	40	1.00
Vascular complications:			
Hematoma	3.3	6.7	0.15
DVT	3.3	0	0.48
Lymphatic complications:			
Lymphorrhea	30	20	0.77
Lymphocele	40	6.7	0.02

SD: standard deviation; DGF: delayed graft function; SCr: serum creatinine; DVT: deep venous thrombosis.

Graft and patient survival rates

In group-I, graft and patient survival at 1, 3, 6, 9 and 12-months were 96.7%, 96.7%, 96.7%, 93.3% and 93.3%, respectively. There were two deaths, first a female died after 3 weeks due to chest infections and AGR. The other was a male recipient died at the 8th month post-KT due to cardiopulmonary complications in spite of a functioning graft. All group-II recipients were alive with functioning grafts at 12-months.

Post-transplant surgical complications

No urinary leakage occurred. Prolonged drain outputs were documented as lymphorrhea. Ureteral strictures, stones, or vesicoureteral reflux did not occur.

Incidence of lymphorrhea in both groups was insignificantly different ($p = 0.77$). Lymphatic leakage ranged from 7 to 21 days either as prolonged drain output or leakage after drain removal. All cases were managed conservatively.

Incidence of lymphocele was significantly lower among patients of group-II ($p = 0.02$). In group-I lymphoceles occurred in 12 recipients (40%). They were small (<150 ml) asymptomatic in 7 (58.3%), medium (150–500 ml) asymptomatic in 3 (25%), and large (>150 ml) symptomatic in 2 recipients (16.7%). Asymptomatic lymphoceles were managed expectantly. One of the large lymphoceles (750 ml) presented by abdominal pain and was treated by percutaneous drainage and sclerotization with a small recurrence that was followed until resolution. The other symptomatic lymphocele (~900 ml) was multilocular and caused graft obstruction. Open marsupialization into the peritoneum was performed successfully.

Hemorrhage, renal artery thrombosis or stenosis did not occur. There was only one case of small peri-graft hematoma in each group which was managed conservatively. Lower limb deep venous thrombosis occurred in one recipient in group-I and was managed conservatively.

Discussion

PLDKT is the optimal strategy for KT-eligible ESRD patients, yet it is still underutilized. However, great enthusiasm lead to increase its rate from 23% to 34% between 1995 and 2009 in USA [9]. The effects of PLDKT on graft function and graft and patient survival have been reported as significant advantages [4]. This is due to avoidance of dialysis-associated morbidity, lower risk of acute and chronic rejections, reduced frequency of DGF, and reduced cardiovascular mortality [3]. However, the difference between PLDKT and LDKT after a short-term dialysis is not yet settled. Also, its effects on other medical and surgical post-KT complications are not widely studied.

The demographic characteristics of our patients were nearly similar to those reported by Kasiske et al., 66.7% were males (33.3% females) and 56.7% of patients had a high educational levels being at college level or higher. They were having private businesses, personal resources or being more employed [4].

The mean age of PLDKT recipients was 44.1 ± 12.1 years and that of donors was 30 ± 6.8 years. This recipient–donor age difference (nearly 14 years) is different from other PLDKT studies that reported similar recipients–donors mean ages (around 40 years). It was also different from recipient–donor age difference in CLDKT where most of related LDs were parents and spouses around 40 years [2,5]. This may be attributed to our exclusion criteria where no extended criteria donors accepted by law.

Similar to other studies, glomerulonephritis represented the commonest primary kidney disease [2,10]. This could be attributed to the relative lower prevalence of diabetes mellitus in our country than in western countries.

Previous studies did not support the rationale of early PKT and found that PKT at higher eGFR was not necessarily associated with better graft and patient survival [11]. In group-I of our study, means of pre-KT serum creatinine and eGFR were 7.96 ± 2.0 mg/dl and 8.27 ± 4.42 ml/min/1.73 m^2, respectively, and we did one session of HD before the operation in 10 patients. This was in agreement with the trend of late PKT [4].

Graft and patient survival

There were no significant differences in the 1-year graft and patient survival rates between both groups. These findings are consistent with Goldfarb-Rumayntzev et al. results where the risk of graft failure reached statistical significance only when the time of pre-KT dialysis was >180 days [8]. Some single-center studies reported no significant differences regardless the pre-KT duration of dialysis [12]. On the contrary, large volume studies showed a significantly better survival rates with PKT than the conventional KT [3,4,7].

In our study, post-KT serum creatinine at different time points was within normal values and similar to other studies which also showed no significant differences between the PLDKT and CLDKT [13,14]. However, mean serum creatinine at 1-month post-KT was significantly lower in group-I. This may be due to more episodes of AGR in group-II in the early post-operative period. This finding cannot be attributed to the residual renal function of native kidneys in group-I, because of the low pre-KT eGFR. Prevalence of graft dysfunction or impaired serum creatinine (>1.5 mg/dL) at 12-months in both groups (8.7% and 6.7%) was lower than other studies as Siddiqi et al. who reported a rate of 54.5–42.3% in LDKT or deceased donor KT (DDKT) [15].

Complications

Non-Surgical Complications:

Delayed Graft Function:

The incidence of DGF is significantly lower in LDKT than in DDKT and in PLDKT than in CLDKT. The values were 2.6% and 6.1% ($p < 0.001$) in PLDKT and CLDKT, respectively, while in preemptive DDKT and conventional DDKT they were 8.4% and 25.6% ($p < 0.001$), respectively [4]. In our study, there was no DGF. In group II, one recipient had 3-hours delay in the function after vascular declamping. This could not be classified as DGF which has been previously defined as the need for dialysis during the first post-KT week, or just failure of the serum creatinine to fall after KT [9]. This very low incidence rate of DGF may be attributed to the benefits of LKD [14]. The suggestion that residual renal function is a cause of low rates of DGF after PLDKT is not applicable in our study as previously discussed.

Acute rejection

Similar to previous studies [5,14], AGR reached a significant difference after 12 months (16.7% for group-I and 46.3% for group-II). However, other single-center studies reported insignificant difference between PLDKT and CLDKT as regards the rates of AGR [3,10].

The duration of pre-KT HD may be the principal cause for the higher rates of AGR in group-II. Other factors like younger ages (more being adolescents), lower education levels that may contribute to non-compliance to immunosuppressive medications and follow-up visits [3] and unrelated donors may contribute to AGR. However, only 1 of the 5 adolescents in group-II had AGR, Also, we had only 2 related donors in our study, so we cannot comment on the effect of these factors on AGR.

Surgical complications

Urinary complications:

In our study, prolonged leaks and peri-graft fluid collections were confirmed to be lymphatic by measuring the creatinine level. The only case of transient ureteral obstruction was relieved by drainage of the causative lymphocele. In our study, absence of major urinary complications may be attributed to careful surgical techniques of graft retrieval and modified Lich-Gregoir ureteroneocystostomy which was reported to minimize surgical complications [16]; placement of JJ stents in all recipients (although controversial) seemed to overcome the effect of odema which is the most common cause of vesicoureteral obstruction [17]; grafts from LDs were associated with less surgical complications when compared with deceased donors [18].

Vascular complications:

Renal artery spasm is a common phenomenon during LDKT due to surgical manipulations. It should be considered in renal grafts with severe ischemia of unknown cause after restoration of vascular flow and it may be misdiagnosed as a sign of hyperacute rejection [19]. Although we used local papaverine during donor nephrectomy and heparin during recipient operation as prophylaxis, renal artery spasm was observed in 4 recipients (3 in group-I and 1 in group-II). All had transient failure of restoration of graft color and consistency for few minutes which relieved spontaneously with immediate diuresis, except the recipient of group-II who needed 3 h to start diuresis.

In both groups, renal vascular thrombosis did not occur. This was reported in LDKT-only studies and may be due to absence of common risk factors such as acute tubular necrosis and DGF [20].

We did not encounter arterial stenosis. This may be due to meticulous end-to-side rather than end-to-end fashion of anastomosis, which is associated with a higher rate of stenosis. Also, LDKT, unlike DDKT, may be considered as a factor against renal artery stenosis [21].

Intra-operative renal vein hemorrhage occurred in one patient due to slipped ligature from the site of left gonadal vein and it was controlled by suturing.

Hematoma may occur immediately post-operative due to anticoagulants. In our study, one small peri-graft hematoma occurred in each group which is consistent with previous studies [22,23].

Lymphatic complications:

Incidence of lymphorrhea was non-significantly different between both groups and most of the leaks were small in amount. Saidi et al. concluded that the incidence of lymphorrhea is higher when grafts procured laparoscopically and in DDKT [24].

In group-I, incidence of lymphocele was 40%. Most of lymphoceles (83.3%) were asymptomatic, while large symptomatic lymphoceles which indicated intervention represented 16.7% similar to other studies [25,26]. In spite of the higher incidence of AGR which was reported as a risk factor for post-KT lymphocele [27], incidence of lymphocele in group-II (6.7%) was significantly lower than group-I. This may be due to: PCKD was the primary kidney disease in 3 of 4 group-I recipients who developed lymphorrhea and/or lymphocele. The effect of PCKD on development of lympahatic complications was controversial, and may be due to the need of simultaneous native nephrectomy; native nephrectomy was done simultaneously in 5 cases *versus* 1 case in both groups, respectively, and this may be due to the possibility to plan pre-KT native nephrectomy in patients who are on regular dialysis.

We managed lymphoceles by percutaneous drainage with sclerotization or surgical marsupialization as suggested by other authors [28].

To the best of our knowledge, this prospective comparative study is the first in Egypt to compare PLDKT with LDKT after a period of dialysis ≤6 months. This study may motivate other investigators to design larger studies on this important subject.

Limitations of our study were (1) small sample size which is mainly due to the low incidence of PLDKT. This issue limited the statistical analysis of survival and different variables' effect on complications; (2) a relatively high percentage of recipients who missed follow-up in group-I (5 cases); (3) late referral to KT centers obliged us to perform one session of dialysis at the night of operation for 10 patients in group-I.

Conclusion and recommendations

PLDKT is slightly different than LDKT after ≤6 months of dialysis with relatively less complications and lower incidence of AGF at 12 months. Taking into consideration that it spares the recipient the morbidities of vascular access and inconveniences of dialysis, PLDKT is recommended as the first choice treatment for each KT candidate. Educational programs should be designed to inform the ESRD patients and their potential LDs about the advantages of PLDKT.

Ethical approval

The ethical committee of the faculty of medicine, Assiut University approved the study.

Conflict of interests

The authors have no conflicts of interests, and have nothing to disclose.

Authors contributions

Rabea Ahmed Gadelkareem, is the main data collector. Diaa A. Hameed, is the corresponding author of this paper. Ahmed M. Moeen, helped with the scientific writing. Ashraf Mahmoud El-Araby, main transplant surgeon in this work. Mostafa Ayman Mahmoud, one of 2 nephrologists that followed up the patients. Ahmed Mohammed El-Taher, supervised the work and helped with scientific writing. Abdolmoniem Abdallah El-Haggagy, developed the research idea and supervised the work. Maher Fouad Ramzy, one of 2 nephrologists that followed up the patients.

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