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Prevention of Poor Early Graft Function Using Open Nephrectomy, and Minimizing the Risk of Procedure-Related Factors

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ABSTRACT

Purpose: To determine the incidence of immediate graft function (IGF), identify events causing delayed graft function (DGF), slow graft function (SGF), and factors that promoted IGF in our living donor transplant recipients using kidneys recovered exclusively by open donor nephrectomy (ODN).

Methods: We performed a recipient- and donor-database analysis after approval from our institutional review board.

Results: Out of 211 recipients, IGF was established in 99.2%, a prolonged recipient warm ischemia time (RWIT) of 112 minutes and severe hypoxia caused DGF (0.4%) and SGF (0.4%), respectively, in 2 recipients. Five grafts were lost, including 3 recipients who died with functioning grafts. A mean 42-month graft survival was 98% in the IGF group and 100% in the poor early graft function (PEGF) group, and small numbers in the PEGF group prevented statistical analysis. The presence of diabetes, black recipients, RWIT of ± 60 minutes, donor warm ischemia time (WIT) of ±5 minutes, multiple arteries, obesity, sensitization, re-transplantation, right kidneys, and female donors did not predispose to PEGF.

Conclusion: We found ODN to be associated with excellent IGF and recommend it. We also recommend minimizing the impact of procedural factors with meticulous vascular anastomoses to reduce RWIT, antithymocyte globulin induction (ATG) to avoid calcineurin inhibitor (CNI) nephrotoxicity, cold histidine-tryptophan-ketoglutarate (HTK) perfusion to reduce cellular injury, and maintain optimal oxygenation and filling pressures in the donor and recipient.

INTRODUCTION

Delayed graft function (DGF) and slow graft function (SGF) continue to plague kidney transplantation despite improvements in surgical techniques and immunosuppression [1]. In deceased donor kidney transplantation (DDKT), there is clear evidence that poor early graft function (PEGF) not only reduces patient and graft survival but also increases the risk of acute rejection that further worsens outcomes [2-5]. However, evidence is also emerging of an unexpected high incidence of DGF and SGF in live donor kidney transplantation (LDKT) with a corresponding negative impact on outcomes [1,6-8]. This is contrary to expectations because organ quality and ischemia times are near ideal compared to DDKT. Additionally, PEGF predisposes these LDKT recipients to higher rates of acute rejection (AR) [1,6], and graft loss [1,6-8], negating the advantage of LDKT. While laparoscopic donor nephrectomy (LDN) is donor friendly, there are legitimate concerns about PEGF in 13-15% [1,6,10-14]. The risk factors for PEGF in LDN include a longer warm ischemia [10] and the negative renal hemodynamic effects of

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Table 1. Recipient and donor characteristics.

Donors: 211	
Age (yrs) M ± SD (range)	32 ± 8 (19-56)
Weight (kg) M ± SD (range)	72 ± 15 (36-126)
BMI > 30 kg/m^2: N (%)	16 (8)
Age > 40 yrs: N (%)	43 (20)
Unrelated: N (%)	47 (22)
Female donor: N (%)	42 (20)
Female donor-to-male recipient: N (%)	17 (8)
Multiple arteries: N (%)	14 (7)
Right kidney: N (%)	43 (20)
Recipients: 211	
Age (yrs) M ± SD (range)	42 ± 16 (4-74)
Black: N (%)	34 (16)
Female: N (%)	78 (37)
Male sex: N (%)	133 (63)
PRA+: N (%)	28 (13)
BMI > 30 kg/m^2: N (%)	12 (6)
Diabetes: N (%)	51(24)
Left-sided transplant: N (%)	16 (6)
Retransplant: N (%)	8 (4)
Calcified artery: N (%)	15 (7)

PRA+: Panel reactive antibody; BMI: body mass index

pneumoperitoneum [11-14]. Surprisingly, however, a similar early graft dysfunction has also been described in other series where the kidneys were recovered by open donor nephrectomy (ODN) [7,15,16]. This suggests that there may also be other procedure-related factors at work besides the mode of allograft recovery.

We undertook this study to determine the incidence of immediate graft function (IGF) in our LDKT cohort where all donor kidneys were recovered by ODN. Additionally, we identified likely factors that promoted IGF and factors that caused PEGF in these recipients.

MATERIALS AND METHODS

All recipients who received kidneys recovered by ODN between June 2007 and December 2011 at the Riyadh Military Hospital, Riyadh, Saudi Arabia were included in this study except those carried out by locum staff. No recipient was excluded because of high immunological risk. All donor kidneys were perfused with cold heparinized histidine-tryptophan-ketoglutarate (HTK) solution and then preserved in standard cold HTK solution for the period of cold ischemia.

Immunosuppression

Induction

Anti-thymocyte globulin (ATG) was used as an induction agent in all recipients who had 3 or more human leucocyte antigen (HLA) mismatches (MM), had prior transplants, or were sensitized. Interleukin 2 antibody induction was used only when MM was 2 or less; methylprednisolone was used in all cases.

Maintenance

This regimen consisted of tacrolimus, mycophenalate mofetil, and glucocorticoids. In the last 2 years, a glucocorticoid-sparing regime was used in recipients who were older, those with diabetes or a family history of diabetes, and those with other cardiovascular and bony complications.

Definitions

Delayed graft function was defined as the need for hemodialysis (HD) in the first week after transplantation. Slow graft function was defined as serum creatinine > 300 µmols/L on day 5 after surgery without dialysis. The presence of DGF or SGF was termed PEGF, or IGF in the absence of both. Follow-up varied between a maximum of 54 months at the start of the series to a minimum of 3 months for transplants carried out in December 2011. The last serum creatinine recorded was at the last clinic visit. Acute rejection (AR) was defined as biopsy-proven acute cellular or antibody mediated rejection, according to prevailing Banff criteria. Donor warm ischemia time (DWIT) was the number of minutes recorded from clamping of the renal artery to submersion in and perfusion with cold HTK solution. Cold ischemia time (CIT) was the time recorded from cold perfusion and storage of the graft to the time of its removal from the preservation solution for implantation. Recipient warm ischemia time (RWIT) or anastomosis time was the time taken to complete the anastomoses. Graft failure was defined as the

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Table 2. Immunological transplant factors.

Living related transplant: N (%)	164 (78)
Living unrelated transplant: N (%)	47 (22)
HLA mismatch < 2: N (%)	11 (5)
3-6 mismatch: N (%)	195 (92)
Zero mismatch: N (%)	5 (2)
ACR: N (%)	11 (5)
AMR: N (%)	7 (3)
ATG induction: N (%)	196 (93)
Sirolimus use: (N)	Zero
Steroid sparing: N (%)	38 (18)

HLA: human leucocyte antigen; ACR: acute cellular rejection; AMR: antibody mediated rejection; ATG: antithymocyte immunoglobulin

need for HD or re-transplantation. Death with a functioning graft was considered a graft loss but did not reflect its quality.

Surgical Procedures

Donor and recipient procedures were performed simultaneously in adjoining operating rooms.

Donor Nephrectomy

All ODNs were performed via a 10 cm flank incision with extraperitoneal access to the kidney. Choice of kidney was decided after considering percentage isotope uptake and vascular anatomy. As an example, if the left kidney had 57% uptake and the right kidney had 2 arteries, we would opt for the right kidney if the vein was suitable. The recipient surgeon would be present in the donor operating room to ensure that the back table preparation was adequate. As soon as the kidney was removed, it was immersed in cold HTK solution and flushed with 500 mL of cold heparinized HTK solution using an olive-tipped metal cannula. In the event of multiple arteries, the main artery was flushed first, followed by the second, and, when needed, the third artery. The lumen of the smaller arteries required flushing with a venous cannula.

Recipient Procedure

Kidneys were typically placed extraperitoneally in the recipient iliac fossa; however, one allograft was placed intraperitoneally in a child weighing 26.45 lbs (12 kg). All vascular anastomoses were end-to-side to the external iliac vessels, except the kidney that was placed within the abdomen where the larger common iliac vessels were used. In 2 cases, end-to-end anastomoses were performed with the inferior epigastric artery for the smaller second renal artery. All multiple arteries were anastomosed independently and the internal iliac artery was not used in any case. All ureteroneocystostomies were extravesical and stented, and stents were removed after 2 weeks under local anesthesia. Furosemide and mannitol were administered intravenously before reperfusion in all cases.

Data Collection and Analysis

After approval from our institutional review board, all donor and recipient data was retrieved. Clinical and laboratory data and patient and graft survival records were accessed individually to ensure graft losses were not missed, and out-patient clinic records were also reviewed. Records of HD in the first week were reviewed in all cases to determine incidence of DGF.

Continuous variables were reported as mean ± standard deviation (range). Categorical variables were reported as an absolute number along with percentages. We used SPSS Version 16.0 (SPSS, Inc., Chicago, IL, USA) software for all statistical analyses. Multiple regression analysis was used to identify risk factors that led to PEGF, and P values of < 0.05 were considered statistically significant.

RESULTS

A total of 211 LDKTs were carried out by the authors during the study period. Immediate graft function was established in 209 (99.2%) recipients while 2 recipients (0.8%) experienced PEGF: 1 DGF and 1 SGF. No grafts were lost because of technical reasons or vascular thrombosis. Recipient and donor data are shown in Table 1. Forty-three donors (20%) were older than 40, the eldest being 56. Female donors accounted for 20% and 7% had multiple arteries. Recipient age varied between 4 and 74; 24% had diabetes, 13% were sensitized, 4% had prior transplants, and calcified arteries were present in 7%. Immunologic and surgical transplant factors are shown in Table 2 and Table 3. Three or more HLA MM was present in 93% of recipients and unrelated transplants were performed in 22%. Donor WIT ranged between 2 to 5 minutes; the longer DWIT of 5 minutes was documented in 3 cases where the artery had to be secured before division of the vein to prevent the dislodgement of clamps. Cold ischemia ranged between 20 to 90 minutes; the mean RWIT was 37 ± 9 and increased to

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Table 3. Surgical transplant factors.

HTK solution used for cold perfusion: N (%)	211 (100)
Donor warm ischemia time M ± SD (range)	2.4 ± 0.6 (2-5)
Cold ischemia time M ± SD (range)	33.9 ± 11.1 (13-90)
Recipient warm ischemia time M ± SD (range)	36.9 ± 9.2 (20-112)
Arterial anastomoses, end to side: N (%)	211 (100)
Two arterial anastomoses: N (%)	13 (6)

HTK: heparinized histidine-tryptophan-ketoglutarate

Table 4. Miscellaneous outcomes.

IGF: N (%)	209 (99.2)
DGF: N (%)	1 (0.4)
SGF: N (%)	1 (0.4)
Donor, length of stay (days): M ± SD (range)	3.1 ± 0.4 (3-7)
Donor, morbidity: N (%)	4 (2); bleeding, 1 surgery
Donor, mortality: N (%)	Zero
Recipient, length of stay (days): M ± SD (range)	6.1 ± 0.7 (4-11)
Recipient, last creatinine (μmols/L): M ± SD (range)	93 ± 61 (24-180)
Recipient, overall mortality: N (%)	3 (1.4)

IGF: immediate graft function; DGF: delayed graft function; SGF: slow graft function

between 50 to 60 minutes in cases with multiple arteries or calcified external iliac arteries. The range of RWIT was 20 to 112 minutes, and the longest tolerated RWIT was 85 minutes in a 37-year-old female receiving her third transplant (left side) with 2 arteries. All multiple arteries were anastomosed independently. Graft function outcomes are shown in Table 4. Of the recipients, 99% had IGF; 205 donors were discharged home on day 3. Table 5 shows serum creatinine (SCr) in μmols/L by the year of transplant. Of 211 recipients, 91% had SCr < 125 μmols/L and 97% had SCr of < 150 μmols/L.

Five grafts were lost: 1 from acute antibody-mediated rejection (AMR), another with hyperacute rejection (HAR), and 3 recipients died with functioning grafts. The first death was in a 30-year-old female who remained comatose following a seizure till her death; the second was a 71-year-old diabetic male who fell while ambulating 3 days after surgery and died of cardiac arrest. The third, a wheelchair-dependent 65-year-old diabetic female died in her sleep 2 months after transplantation. One recipient with calcified iliac vessels was explored but not transplanted.

A 38-year-old female recipient who received the kidney from her 42-year-old genetically unrelated husband developed DGF. Initial graft perfusion was patchy but improved after revision of the arterial anastomosis, for a collective RWIT of 112 minutes. Urine output and renal function improved after 2 sessions of HD. On day 7, she tested positive for H1N1 and required ventilator support with regular HD and all immunosuppression was withdrawn. After 5 weeks, with improvement in her pulmonary function, the allograft started producing urine. A graft biopsy was reported as normal, gentle immunosuppression was reintroduced, and 34 months later, her serum creatinine was 63 μmols/L. The SGF recipient had initial IGF but was prematurely extubated at the end of surgery and required re-intubation and ultrafiltration. She did not require HD, and her serum creatinine (SCr) on day 5 was 347 μmols/L, and her SCr after 28 months was 98 μmols/L.

DISCUSSION

In this retrospective LDKT study where all kidneys were recovered with ODN, 99% of recipients had IGF. We were unable to statistically identify any risk factors due to the very low incidence of PEGF in only 2 recipients out of 211 (0.8%). The probable causes of PEGF were a prolonged RWIT (DGF) and severe hypoxia (SGF) in 1 recipient each, and both recipients who lost their grafts from AMR and HAR had initial IGF. The concern that early renal injury, even if minor (SGF) may negatively impact long-term outcomes appears justified because of the overwhelming evidence in DDKT [2-5,17]. Similar evidence in LDKT negates its advantages because the benefits of IGF, reported by several authors, are lost [1,6,8,9,14]. Recipients with either DGF or SGF have double the risk for graft failure, have inferior renal function at 1 year, worse rejection-free survival and are less likely to survive 5 years [6]. A large study of 2,500 LDKT recipients found DGF to be associated with worse allograft function and survival [8]. The 2005 OPTN/SRTSR annual report was alarming in that 1 year of LDKT graft survival was only 65% in cases with DGF, compared to an amazing 97% in recipients with IGF [9].

The incidence of PEGF in the recent LDKT literature is between 13% [1] and 16% [6,7] compared to < 1% in our study; this would suggest that it is possible to significantly reduce, if not

Table 5. Serum creatinine (S Cr) in µmols/L by year of transplant.

Year	Total	Follow-up months	S Cr < 100	S Cr 100-125	S Cr 126-150	S Cr 151-180
2007	23	51-57	17	4	2	0
2008	37	39-51	28	3	1	4
2009	47	27-39	39	5	2	1
2010	47	15-27	33	9	3	1
2011	57	3-15	44	10	3	0
N (%)	211 (100)		161 (76)	31 (15)	11 (6)	6 (3)

completely avoid, PEGF. The importance of this statement is that a PEGF incidence of 10 to 15% should no longer be acceptable. The number of recipients in our series is smaller than the quoted series, but with our strategy, we are confident we can achieve the same results in a larger cohort. We do not have a selection bias, and our cohort is not a low-risk cohort and includes recipients with high immunological and surgical risk. The former included 92% recipients with 3 to 6 MM, sensitization (13%), prior transplants (4%), black race (16%), and genetically unrelated pairs (20%). The surgical high-risk recipients included 24% with diabetes, calcified arteries (7%), right kidneys (20%), obesity, and left-sided transplants (6%). Two studies that used LDN reported high rates of PEGF [1,6]; in contrast, our PEGF rate was < 1% with exclusive ODN. We found studies reporting similar PEGF rates with LDN and ODN surprising, because it suggested that PEGF did not entirely depend on the mode of allograft recovery, but that perhaps the importance of other procedure-related risk factors may not have been fully appreciated [7,9,15,16]. The comparison between ODN and LDN in these studies lacked objectivity, because crucial data such as WIT in ODN cases was not available in one study [15], while the other study did not discuss this comparison at all [7].

In our study, minimizing the impact of procedure-related factors was considered as important as ODN in avoiding PEGF, because their collective benefit perhaps promoted IGF in our recipients. Donor WIT was reduced with ODN, and RWIT was kept to a minimum with meticulous vascular anastomoses. Cellular injury from cold ischemia was reduced by using an HTK solution for perfusion and storage. Calcineurin inhibitor (CNI) nephrotoxicity was avoided at the time of reperfusion with ATG induction because tacrolimus was started only after graft function was established. Appropriate donor and recipient filling pressures were maintained at the time of kidney recovery, and reperfusion and hypoxia was prevented with attention to perioperative detail.

Any procedure used to recover living donor kidneys must be absolutely safe, have zero mortality, fulfill expectations and deliver a kidney capable of immediate function in the recipient. We have shown this to be the case with ODN in our series because none of the 2 cases of PEGF were related to the recovery procedure. Despite better quality and shorter CIT, the claim in some LDN studies that live donor kidneys were able to recover from LDN procurement-related insults [6,18] was not substantiated in a longer follow-up [1,6]. In contrast, we feel that ODN was the main reason for our high rates of IGF; the argument that only donors who undergo LDN have a short hospital stay is no longer valid because the length of stay in 97% of our donors with ODN was similar to that reported in two LDN series [1,6] and UNOS data for LDN [19]. There is ample evidence in the literature linking PEGF to LDN [1,6,10,11,14] but surprisingly the procedure continues to be promoted, and perhaps for the same reasons it is unlikely that any large, randomized, controlled trial will ever be carried out to assess its effect on long-term outcomes [18]. This preference for LDN unfortunately is also not evidence-based but driven largely by donor sentiment [20] and strong market and industry needs [18]. It would otherwise be difficult to understand why it would be preferred over ODN despite its association with a higher vascular [21] and ureteric [22] complication rate, and PEGF [1,6]. Additionally, histological evidence in zero hour biopsies in kidneys recovered by LDN demonstrated subcapsular degeneration, necrosis of tubular cells, a congestion of glomerular and peritubular capillaries associated with hemorrhage, and fibrin deposits in the renal capsule. These findings were observed in 35 out of 65 LDN specimens (54%) but in the same study, no such changes were demonstrated in any of the 43 donor kidneys recovered by ODN [11]. In a 2007 literature review, Shokeir et al. [23] found that LDN had the disadvantages of increased operative time, increased warm ischemia, and increased major complications requiring reoperation along with underreporting of unfavorable results [23]. An increased risk for a combined endpoint of intraoperative incidents, major complications, and significant bleeding were observed in LDN [24]. The cost of LDN was twice that of ODN, and the greatest cost difference was related to dealing with its complications [25]. Despite

the enthusiasm for LDN, Kranenburg only found 25% of the general population in its favor [26], and at present, there is no strong evidence that LDN is better than ODN [27].

We think the likely events associated with PEGF in our cohort were identified because of their critical timing and nature. The DGF was caused by an extended RWIT of 112 minutes and the SGF by severe hypoxia. With a meticulous surgical technique in the former and better attention to perioperative detail in the latter, PEGF could have been completely avoided. Sixty minutes of RWIT in cases with thick and calcified arterial walls and anastomosis in multiple arteries did not cause PEGF in our series. The main reason for the low incidence of PEGF in our series appears to be a short DWIT. It was under 2 minutes in over 90% because of ODN and only 2% of the 211 donor kidneys had an unavoidable WIT of 5 minutes because the arterial stump had to be secured before dividing the vein to prevent dislodgement of the arterial clamp. That a WIT of 5 minutes was tolerated suggests that the absence of the pneumoperitoneum and optimized procedural factors may have compensated for the longer DWIT. The combination of a longer DWIT and pneumoperitoneum in LDN may be the reason for the higher incidence of PEGF in these studies [1,6,9-14].

At least 2 groups found an increased risk of AR in recipients with PEGF7 [14,18]; however, neither of our 2 PEGF cases experienced AR, despite the fact that the recipient with DGF was off routine immunosuppression because of H1N1. Both recipients had excellent graft function at 28 and 34 months, respectively.

Some teams flushed kidneys with heparinized Ringers Lactate and saline solutions [1,7] we used heparinized HTK solution for all our allografts. Another series where all kidneys were recovered exclusively by LDN also used UW or HTK solution, but with substantial PEGF [6]. The major difference in this series and ours was the method of kidney recovery (LDN or ODN), indicating that although the role of the preservation solution in LDKT may be considered minor because of the short CIT, the combined effect of minimizing several minor factors in our study may have prevented PEGF and facilitated IGF.

We have relied heavily on ATG for induction (93%) along with methylprednisolone because of a high immunological risk in our cohort. Some clinicians have a tendency to start tacrolimus preoperatively in cases where ATG induction is not used, but because of our confidence in ATG, we avoided preoperative CNIs. The profound lymphopenia with ATG prevented AR and allowed gentle introduction of tacrolimus once graft function was established. In analyzing UNOS data from 2000, Troppmann found early CNI inhibitor dosing to be a factor that may have affected both the short-and long-term outcomes [19].

This is an important study because it presents a strategy that has been very successful in preventing DGF and SGF in LDKT. There is nothing novel about this strategy. We persevered with ODN and minimized the risk from all other procedure-related factors. This combination achieved an IGF rate of 99% compared to 84 to 90% in the current literature [1,6,7]. No graft was lost from vascular complications in 211 transplants, and we attribute this to a meticulous surgical technique. This is a personal series and may not be reproducible, but we have shown that achieving IGF in every case is not altogether impossible. It would be understandable to expect a degree of skepticism, given that these results are being reported from the developing world. The recipient and donor procedures were carried out simultaneously. One recipient surgeon did all implantations and the donor surgeon, all the nephrectomies. Both surgeons maintained good communication, and interestingly, when an appendicular mass was discovered in 1 of our recipients, the donor surgery was halted till it was deemed safe to proceed with the transplant following appendectomy [28]. We admit that our follow-up is short, however, since our first objective was to determine the rate of IGF (based on the graft function in the first postoperative week). The range of follow-up of 3 to 54 months was deemed adequate to illustrate the trend of graft function. Mean recipient SCr was 93 ± 61, range 24 to 180 μmols/L. It is interesting that no recipient from 2007 with the longest follow-up had SCr >150 and 97% of all 211 recipients had SCr of < 150 μmols/L (Table 5).

In conclusion, in this single-center retrospective LDKT study where all donor allograft recovery was carried out by ODN, we achieved IGF in 99% of recipients. Since both events associated with PEGF were preventable, a zero incidence of PEGF would always be achievable. Based on this experience with excellent IGF, we recommend a strategy that includes ODN, simultaneous donor and recipient procedures, cold perfusion with HTK, good surgical technique, ATG induction, and optimal donor and recipient hemodynamics.

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