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INTEGRATED STRATEGY FOR PREVENTING DELAYED RENAL GRAFT FUNCTION

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Objective: to determine the efficacy and safety of an integrated strategy aimed at preventing delayed renal graft function (DGF). **Materials and methods.** From June 2018 to December 2022, 478 deceased-donor kidney transplants were performed at Botkin Hospital, Moscow. The patients were divided into two groups: Group I consisted of 128 patients who did not use the integrated strategy; Group II included 67 patients in whom the DGF prevention strategy was used at the perioperative stage. The integrated strategy involved the use of hypothermic oxygenated machine perfusion (HOPE) using expanded criteria donors, the use of a second warm ischemia (SWI) elimination device, personalized initial calcineurin inhibitor (CI) dosing, and use of alprostadil for high vascular resistance in renal graft arteries. **Results.** DGF occurred in 5 of 44 patients (11.4%) that used the integrated strategy, and in 13 of 44 patients (29.5%) in the control group. The differences were statistically significant ($p = 0.034$), there was a medium strength relationship between the traits ($V = 0.225$). The use of the integrated DGF prevention approach reduced the chances of developing DGF by a factor of 0.3 (95% CI: 0.1–0.95). The risk of DGF in the integrated strategy group was 61.3% of the risk of DGF in the non-strategy group, thus the relative risk (RR) is 1.63 (95% CI: 1.1–2.4). Median duration of graft function normalization was statistically significantly lower in group II: 5 (IQR: 3–9) versus 15 (IQR: 7–19) days ($p = 0.012$). Mean length of hospital stay was 19.1 ± 4.2 (95% CI: 14.5–26.1) bed-days in group I and 13.9 ± 3.4 (95% CI: 9.3–17.2) bed-days in group II. Differences in this indicator were also statistically significant ($p = 0.043$). **Conclusion.** The set of DGF prevention measures, developed at Botkin Hospital, evidence-based and implemented in clinical practice, can reduce the burden of modifiable risk factors of this complication significantly, thereby improving treatment outcomes for kidney transplant recipients considerably.

Keywords: kidney transplantation, delayed renal graft function, risk factors.

INTRODUCTION

According to 2021 annual data report from the United States Renal Data System (USRDS), the 5-year graft survival rate for recipients of kidney from a deceased donor was 77.6%, compared to 46.5% and 41.7% for patients on peritoneal dialysis and hemodialysis, respectively. Improvement in surgical technique, achievements in transplantation immunobiology, increased availability of kidney transplantation (KTx) as a result of better organ donation coordination [1–4], have made KTx the gold standard for treatment of patients with end-stage chronic kidney disease (CKD) without absolute contraindications [5, 6].

Organ shortage is a global problem in clinical transplantology. One of the justified steps to reduce its burden is the expansion of the donor pool through suboptimal donors (expanded criteria donors) [7]. The donation criteria expansion strategy, on one hand, allows increasing the availability of transplant care. On the other hand, however, the use of transplants obtained from suboptimal donors is associated with increased incidence of postoperative complications and shorter duration of graft functioning, which has been reported by many authors. One of such complications is DGF, which is associated both with a higher number of early postoperative complications and with worse long-term renal graft survival outcomes [8].

Previously, we have identified potentially modifiable risk factors for DGF [8] and preventive measures were developed for each of them to reduce their impact on renal graft [9–13].

The next stage of our work was to evaluate the effectiveness of the integrated strategy, which consisted of the combined use of HOPE, use of an SWI elimination device, personalized initial CI dosing, and use of alprostadil for high vascular resistance.

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MATERIALS AND METHODS

From June 2018 to December 2022, 478 deceased-donor kidney transplants were performed at Botkin Hospital, Moscow.

Patients were divided into two groups: Group I consisted of 128 patients in whom the integrated DGF prevention strategy was not applied; Group II included 67 patients who used the strategy. Patient mean age was 46.91 ± 9.9 (20–70) years. There were 49 women, mean age was 46.26 ± 9.4 (20–71) years. Men were 79, mean age was 47.14 ± 10.1 (20–71) years. All patients were diagnosed with stage 5 CKD. CKD developed in 72 patients (56.3%) against chronic glomerulonephritis, in 9 patients (7%) as a result of autosomal dominant polycystic kidney disease (ADPKD), in 8 patients (6.3%) as a result of diabetic nephropathy, in 7 patients (5.5%) as a result of chronic pyelonephritis, in 7 patients (5 in 6 (4.7%) against urogenital anomaly, in 5 patients (3.9%) against nephroangiosclerosis, in 5 patients (3.9%) against urolithiasis, in 5 patients (3.9%) against hemorrhagic vasculitis, and in 4 patients (3.0%) against focal segmental glomerulosclerosis. There were 99 patients (77.3%) on hemodialysis, 23 patients (17.9%) on peritoneal dialysis, and 6 patients (4.8%) on predialysis. Preoperative diuresis was present in 81 patients (63.2%) and absent in 47 (36.8%). This was the first KTx for 107 patients (83.6%), the second for 20 (15.6%) patients, and the third for 1 (0.8%) patient. Median recipient BMI was 25.08 (IQR: 21–33) kg/m^2. Increased levels of preexisting class I antibodies were observed in 6 patients (4.7%), and class II in 8 patients (6.3%).

In all cases, KTx was performed from a deceased donor. The kidney donor was recognized as a standard donor in 86 cases (67.2%), as an expanded criteria donor in 40 cases (31.3%) and as a donor after cardiac death in 2 cases (1.5%). Median donor age was 47 (IQR: 41–55) years and BMI was 26.2 (IQR: 24.0–31.1) kg/m^2. Median creatinine levels and ICU length of stay were 87.37 (IQR: 70–93) μmol/L and 43 (IQR: 32.3–78.1) hours, respectively. Vasopressor support was used in 101 donors (78.9%), among whom 4/101 (3.9%) had a norepinephrine dose >1000 ng/kg/min or a second vasopressor was connected.

Median cold storage time was 10.1 (IQR: 8.2–12.5) hours. Median SWI time (vascular anastomosis formation) was 41 (IQR: 31–51) minutes. Mean operative time and intraoperative blood loss were 221.3 ± 44.5 (95% CI: 226.5–244.2) minutes and 115.3 ± 75.2 (95% CI: 113.4–134.2) mL, respectively. In all cases, intraoperative Doppler ultrasound of the renal graft was performed with determination of arterial resistivity index (RI), the median of which was 0.7 (IQR: 0.63–0.85). A standard technique was used to reduce the effect of SWI. A triple-therapy regimen consisting of prolonged-release tacrolimus, mycophenolic acid derivatives and methylprednisolone was used in all cases as immunosuppressive therapy in the early postoperative period. Basiliximab was used intraoperatively in all cases for induction and on day 4. Similarly, 500 mg of methylprednisolone was administered intraoperatively on days 3 and 5. The target tacrolimus trough level in the early postoperative period was 10–12 ng/mL.

Group II included 67 patients in whom the integrated strategy to the prevention of DGF was used at the perioperative stage. Mean patient age was 45.53 ± 10.7 (20–71) years. There were 22 women, the mean age was 45.43 ± 10.6 (21–72) years. Men were 45, mean age was 45.67 ± 10.1 (20–72) years. All patients were diagnosed with stage 5 CKD. In 35 patients (52.3%) CKD developed against chronic glomerulonephritis, in 8 patients (11.9%) against ADPKD, in 8 patients (11.9%) against diabetic nephropathy, in 6 patients (9%) against chronic pyelonephritis, in 6 patients (9%) against chronic tubulointerstitial nephritis, and in 4 patients (5.9%) against urogenital anomaly. There were 59 patients (88%) on hemodialysis, 6 patients (9%) on peritoneal dialysis, and 2 patients (3%) on predialysis. Preoperative diuresis was present in 52 patients (77.6%) and absent in 15 (22.4%). This was the first KTx for 64 patients (95.5%) and the second for 3 (4.5%) patients. Median recipient BMI was 25.66 (IQR: 21–32) kg/m^2. Increased levels of preexisting class I antibodies were found in 4 patients (5.9%), and class II in 7 patients (10.4%).

In all cases, KTx was performed from a deceased donor. The kidney donor was recognized as a standard donor in 35 cases (52.2%), as an expanded criteria donor in 26 cases (38.8%) and as a donor after cardiac death in 6 cases (9%). Median donor age was 49.6 (IQR: 45–56) years and BMI was 26.9 (IQR: 24.6–31.3) kg/m^2. Median creatinine levels and ICU length of stay were 89.9 (IQR: 74–98) μmol/L and 45 (IQR: 32.3–78.1) hours, respectively. Vasopressor support was used in 56 donors (83.5%), among whom 4/56 (7.1%) had a norepinephrine dose >1000 ng/kg/min or a second vasopressor was connected.

The average perfusion time was 211.35 ± 42.67 (180–320) minutes. When perfusion was performed, median static hypothermic preservation time was 278.35 ± 94.26 (250–450) minutes. Median SWI time (vascular anastomosis formation) was 40 (IQR: 31–52) minutes. A device developed at the clinic was used to reduce the effect of SWI. Mean operative time and intraoperative blood loss were 219.3 ± 45.3 (95% CI: 214.7–249.5) minutes and 117.9 ± 74.1 (95% CI: 115.3–140.9) mL, respectively. In all cases, intraoperative Doppler ultrasound of the renal graft was performed with determination of RI, the median being 0.76 (IQR: 0.6–1). To correct RI, patients in this group received continuous infusion of alprostadil at a dose of 120 μg per day. A triple-therapy regimen consisting of prolonged-release tacrolimus, mycophenolic acid derivatives and methylprednisolone was used

in all cases as immunosuppressive therapy in the early postoperative period. Basiliximab was used for induction in all cases intraoperatively and on day 4. Basiliximab was used intraoperatively in all cases for induction and on day 4. Similarly, 500 mg of methylprednisolone was administered intraoperatively on days 3 and 5. The starting tacrolimus dose taken by the patient before surgery was determined individually based on the patient's age and weight. Target tacrolimus trough level in the early postoperative period was 10–12 ng/mL.

Methods and statistical analysis

The exclusion criteria for both groups were the following: primary nonfunction, postoperative complica-

Table 1

Comparative characteristics of perioperative factors in groups I and II

Indicator	Group I (n = 128)	Group II (n = 67)	p
Sex: *Male* *Female*	 80 48	 44 22	0.871
Average age (years)	44.34 ± 13.47	45.53 ± 10.7	0.981
Diagnosis: *Chronic glomerulonephritis* *Polycystic kidney disease* *Diabetic nephropathy* *Chronic pyelonephritis* *Chronic tubulointerstitial nephritis* *Urolithiasis* *Developmental anomaly* *Hemorrhagic vasculitis* *Hypertensive nephroangiosclerosis*	 75 12 11 8 7 3 7 2 2 1	 35 8 8 6 6 0 4 0 0 0	0.645
Diuresis: *Adequate* *Oligoanuria*	 83 45	 52 15	0.798
Dialysis: *Hemodialysis* *Peritoneal dialysis* *Pre-dialysis patient*	 98 22 8	 59 8 2	0.674
Transplant history: *First transplantation* *Second transplantation* *Third transplantation*	 109 19 0	 64 3 0	0.791
Increased pre-existing antibodies: *Class I* *Class II*	 8 9	 4 7	0.77
Recipient median body mass index (kg/m^2)	24.26	25.66	0.453
Donor type: *Standard DBD donor* *Expanded criteria DBD donor* *DCD donor*	 83 44 1	 35 26 6	 0.56 ***0.007**
Donor median age (years)	42.3	49.6	***0.042**
Donor median body mass index (kg/m^2)	24.7	26.9	0.85
Donor median creatinine level (μmol/L)	88.2	89.9	0.873
Donor median length of hospital stay (hours)	47	45	0.76
Donor vasopressor support: *No* *Yes*	 19 109	 11 56	0.59
Mean total hypothermic preservation time (static + oxygenated perfusion) (minutes)	661.45 ± 159.4	649 ± 123.8	0.341
Average hypothermic oxygenated machine perfusion (minutes)	0	214.7 ± 49.1	***<0.001**
Median second warm ischemia time (minutes)	43	40	0.74
Mean surgical time (minutes)	239.2 ± 51.4	219.3 ± 45.3	0.125
Median blood loss volume (mL)	134.3 ± 82.9	117.9 ± 74.1	0.229
Median intraoperative resistive index	0.72	0.73	0.94

tions requiring emergency graftectomy in the first week after transplantation, and recipient death in the first 7 days. The groups were comparable in terms of basic recipient characteristics, perioperative parameters, and a number of donor characteristics except for age ($p = 0.042$) and proportion of asystolic donors ($p = 0.007$). Detailed comparative characteristics are presented in Table 1.

Due to significant differences in two important risk factors for DGF – donor age and frequency of donors after cardiac death (DCD) ($p = 0.047$ and $p < 0.001$, respectively) – we performed pseudorandomization of the compared groups by PSM (0.1 compliance (or matching or conformity) tolerance). The resulting pseudorandomization groups had 44 patients each and were comparable for donor age ($p = 0.732$) and proportion of DCD donors ($p = 0.612$).

RESULTS

Analysis of the immediate results in the two study groups after pseudorandomization showed that DGF developed in 5 of 44 patients (11.4%) in the integrated strategy group, and in 13 of 44 patients (29.5%) in the control group. The differences were statistically significant ($p = 0.034$) and there was a medium strength relationship between the traits ($V = 0.225$). The use of the integrated preventive strategy reduced the chances of developing DGF by a factor of 0.3 (95% CI: 0.1–0.95). The risk of DGF in the integrated strategy group was 61.3% of the risk of DGF in the group that did not use the strategy, thus RR = 1.63 (95% CI: 1.1–2.4). Median duration of graft function normalization was statistically significantly lower in group V: 5 (IQR: 3–9) versus 15 (IQR: 7–19) days ($p = 0.012$). Mean length of hospital stay was 19.1 ± 4.2 (95% CI: 14.5–26.1) bed-days in group I and 13.9 ± 3.4 (95% CI: 9.3–17.2) bed-days in group V. Differences in this indicator were also statistically significant ($p = 0.043$).

Clinical outcomes of treatment of kidney recipients in groups I and II before and after pseudorandomization are presented in Table 2.

DISCUSSION

DGF is a multifactorial problem that has a significant negative impact on both immediate and long-term outcomes of KTx. This complication is enhanced significantly by donor characteristics that transplant physicians cannot correct. At the same time, there are a number of factors that can have an additional damaging effect on the renal graft at the stage of preservation (static hypothermic preservation time), surgery (SWI time) and in the early postoperative period (nephrotoxicity of CIs, increased vascular resistance). The more donor-associated risk factors for DGF, the more attention should be paid to the correction of perioperative risk factors.

In our opinion, correction of potentially modifiable risk factors should be carried out at all the above stages – preservation, surgery and in the early postoperative period – since mitochondrial damage in kidney graft cells can be prevented using HOPE, but severe ischemia-reperfusion injury can be caused due to prolonged SWI with development of high vascular resistance with impaired perfusion of the renal graft cortex. On the other hand, a short SWI time and a perfectly selected initial CI dose are not able to prevent severe ischemia-reperfusion injury during prolonged static hypothermic preservation with cell organelle death.

Clinical data obtained demonstrate the benefits of our integrated DGF prevention strategy, which consists of the use of HOPE for expanded criteria donors, the use of an SWI elimination device, personalized initial CI dosing, and the use of alprostadil for high vascular resistance in renal graft arteries. There was a significant decrease in DGF incidence ($p = 0.034$) and median duration of DGF ($p = 0.012$) compared with the control group. This led to shorter average length of hospital stay ($p = 0.043$).

CONCLUSION

The set of DGF prevention measures, which were developed at Botkin Hospital, evidence-based and implemented in clinical practice, can reduce the burden of modifiable risk factors of this complication significantly,

Table 2

Comparative analysis of treatment outcomes in groups I and II before and after pseudorandomization

Indicator	Pre-pseudorandomization			Post-pseudorandomization		
	Group I (n = 128)	Group VI (n = 67)	p	Group I (n = 44)	Group VI (n = 44)	p
Donor median age (years)	42.3	49.6	***0.042**	46.7	47.1	0.732
Proportion of asystolic donors	1/128 (0.8%)	6/67 (9%)	***<0.001**	1/44 (2%)	3/44 (7%)	0.612
Frequency of DGF	37/128 (28.9%)	15/67 (22.4%)	0.609	13/44 (29.5%)	5/44 (11.4%)	***0.034**
Median DGF duration (days)	13	6	***0.029**	15	5	***0.012**
Average length of hospital stay (bed-days)	16.21 ± 8.4	15.37 ± 4.2	0.312	19.1 ± 4.2	13.9 ± 3.4	***0.043**
Incidence of all complications	22/128 (22%)	6/67 (8.9%)	0.134	12/44 (27.3%)	3/44 (6.8%)	0.27
Incidence of acute graft rejection	0	1/67 (1.4%)	0.89	0	0	1
In-hospital mortality	0	0	1	0	0	1

thereby improving treatment outcomes for kidney transplant recipients considerably.

The authors declare no conflict of interest.

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