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Risk factors and consequences of delayed graft function in renal transplantation

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The study approved by the Ondokuz Mayis University Clinical Research Ethics Committee (Approval number: 2020/510).
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

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Abstract

Background/Aim: Delayed graft function (DGF) continues to be an important complication in patients who underwent kidney transplantation. Our study aimed to determine the rate of DGF and risk factors after renal transplantation at our center and explore DGF-related complications and outcomes.
Methods: Patients over 18 years of age who underwent kidney transplantation between January 2015 and January 2020 were evaluated. DGF was defined as the need for at least one dialysis session within the first week after renal transplantation. The factors affecting DGF were analyzed as the primary outcome, and discharge and additional complications, as the secondary outcomes.
Results: Data of 206 patients who underwent renal transplantation were analyzed, and delayed graft function (the need for at least one dialysis session within the first week after renal transplantation) was observed at a rate of 20.9%. A statistically significant relationship was observed between DGF and presence of diabetes mellitus, cadaver graft transplantation, higher cold ischemia time, need for postoperative erythrocyte suspension and fresh frozen plasma transfusion ($P<0.05$ for all). Graft loss was significantly higher in patients with DGF ($P=0.001$).
Conclusion: After renal transplantation, delayed graft function continues to occur at a high rate. Prevention of delayed graft function development will reduce graft loss rates.

Keywords: Kidney transplantation, Delayed graft function, Allograft rejection

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Introduction

Most cadaveric and some living-donor organ transplants show early dysfunction to some extent, leading to delayed graft function (DGF). Rarely, the graft never functions (primary dysfunction). DGF is a form of acute renal failure that results in post-transplantation oliguria. Optimization of donor and recipient management and improvements in diagnostic and therapeutic modalities have neither reduced the overall rates of this disorder nor mitigated its short- and long-term effects [1]. DGF is associated initially with ischemia-reperfusion injury, and triggered host inflammatory response and, ultimately, with decreased graft life and patient survival, and acute graft rejection [2]. The factors that affect DGF can be grouped as donor-related, recipient-related, and perioperative risk factors [3, 4].

Our aim in the study was to determine the rate of DGF and risk factors after renal transplantation at our center and explore DGF-related complications and outcomes.

Materials and methods

Our hospital's patient data system "Nucleus Medical System^{R}" and archived data records were used to retrieve data of patients who underwent renal transplantation at Ondokuz Mayıs University Medical Faculty Hospital between January 2015 and January 2020. It was a retrospective study approved by the Ondokuz Mayis University Clinical Research Ethics Committee (Approval number: 2020/510). The exclusion criteria were as follows: Being aged <18 years, mortality within the first week, inability to access screening data related to DGF, the presence of concomitant extra renal organ transplantation, and primary dysfunction after renal transplantation. All patients aged >18 years who underwent living-donor or cadaveric renal transplantation were included in this study.

DGF was defined as the need for at least one dialysis session within the first week after renal transplantation.

The following data were recorded: Patient demographics (e.g., age, body mass index (BMI), chronic diseases, and drugs used), human leukocyte antigen (HLA) matching, drugs used in anesthesia induction and their doses, drugs used in anesthesia maintenance and their doses, intraoperative fluid amounts, blood and blood products, inotropic and/or antihypertensive drugs and their doses, intraoperative vital signs (e.g., arterial blood pressure, pulse, body temperature, respiratory rate, SpO2, central venous pressure, and mechanical ventilation values), vital signs in the first postoperative week (e.g., arterial blood pressure, pulse, number of respiration, and body temperature), SpO2, daily urine amount, electrolyte values (Na, K, Mg, Cl, P, Ca), total blood count, blood urea nitrogen, creatinine values, daily and total postoperative fluid balance, blood and blood products used, and inotropic and/or antihypertensive drugs and their doses. Immunosuppressive protocol used after transplantation, and dialysis requirements in the first postoperative week were examined in terms of DGF. Parameters considered to affect DGF were evaluated by comparing them with the data of the non-DGF control group.

Statistical analysis

Demographic data were summarized using frequency (percent) or mean (standard deviation) depending on the data type. Fisher's exact tests and chi-squared tests were used to compare categorical variables, and one-way analysis of variance was used to compare continuous variables. Logistic regression models were utilized to assess the risk factors for mortality, graft loss, and DGF. Statistical analyses were performed using IBM SPSS Statistics 21.0 software. $P<0.05$ was considered statistically significant.

Results

The data of 206 patients who underwent renal transplantation were accessed. DGF was observed in 43 (20.9%) patients. Evaluation of the relationship between DGF and demographic data, HLA matching, and comorbidities revealed that DGF rates were higher in the presence of diabetes mellitus ($P=0.007$); however, there was no significant correlation between DGF and the other variables (Table1). Patients were not evaluated in terms of ABO blood group matching, as fully matching ABO group was a prerequisite for renal transplantation at our center. In total, 106 (51%) patients underwent cadaveric renal transplantation, while 100 (49%) underwent living-donor renal transplantation. Among the live donor transplants, 62 (62%) were first degree, 34 (34%) were second degree, 4 (4%) were third-degree relatives. No intraoperative or postoperative complications were encountered in transplants from living donors. There has been no mortality in living donors so far. DGF was observed in three (3%) recipients of living-donor kidneys and in 40 (37.7%) recipients of cadaveric kidneys ($P=0.011$). The mean cold ischemia times were 379 (60–1.140) minutes and 721 (70–1.200) minutes in the living and cadaveric donor groups, respectively, with a significant correlation between cold ischemia time and DGF ($P<0.01$). However, DGF was not significantly correlated with surgery duration, intraoperatively used crystalloid and colloid quantity, blood and blood product transfusion, or the rates of hypo- and hypertensive attacks developing intraoperatively (Table 2). According to the renal transplantation protocol followed at our center, regardless of patient weight, all adult patients were administered 500 mg methylprednisolone, 12.5 g mannitol, and 100 mg furosemide during the operation. Methylprednisolone, mannitol, and furosemide and their doses per kilogram of patient weight were studied to see if they correlated with DGF, but no significant difference was noted (Table 2). Of all patients included,192 (93.2%) underwent open and 14 (6.8%) underwent laparoscopic renal transplantation. The rate of DGF was significantly higher in patients who underwent laparoscopic renal transplantation ($P=0.026$). When the hemoglobin level, blood and blood product transfusions, and hemodynamic parameters of the patients undergoing renal transplantation were analyzed during the first postoperative week, DGF was found to significantly correlate with receiving freshly frozen plasma and erythrocytes suspension replacement ($P<0.05$), but not with the other variables (Table 3).

In patients with DGF, graft rejection rate was significantly higher ($P<0.05$) compared to those without DGF, while mortality rate and the duration of hospitalization were similar (Table 3).

Table 1: The relationship between demographic data and delayed graft function

	DGF (+) n=43	DGF (-) n=163	*P*-value
Age, year (mean,min-max)	44 (20-60)	42 (18-66)	0.364
BMI, kg/m^2 (mean, min-max)	23.4 ((14.8-32.8)	23.5 (14.1-35.4)	0.359
Sex (Female/Male) %	41.9/58.1	58.1/41.9	0.493
Diabetes Mellitus %	51.2	35.6	0.007
Hypertension %	51.2	50.9	0.623
Heart failure %	4.7	3.7	0.314
COPD %	0	1.2	0.999
Smoke %	37.5	9.2	0.062
HLA mismatches (%)			0.305
0	8 (18.6)	15 (9.2)	
1	8 (18.6)	36 (22.1)	
2	9 (20.9)	39 (23.9)	
3	12 (27.9)	42 (25.8)	
4	5 (11.6)	19 (11.7)	
5	-	2 (1.2)	
6	1 (2.3)	10 (6.1)	

COPD: Chronic Obstructive Pulmonary Disease, BMI: Body Mass Index, HLA: Human Leukocyte Antigen

Table 2: The relationship between intraoperative data and delayed graft function

	DGF (+) n=43	DGF(-) n=163	*P*-value
Surgery time, minute	225 (155-480)	209 (110-480)	0.075
Intraoperative crystalloid amount, ml	3045 (2000-5500)	2975 (1000-6000)	0.465
Intraoperative colloid%	7	8	0.684
Erythrocyte Suspension%	4.7	7.4	0.999
Fresh Frozen Plasma%	4.7	2.5	0.999
Intraoperative Hypotension%	16.3	14.1	0.606
Intraoperative Hypertension%	7	8	0.749
Steroid (mg / kg)	7.9 (5-14.2)	8.7 (3.7-26.3)	0.186
Mannitol (g / kg)	0.19 (0.01-0.37)	0.19 (0.01-0.39)	0.323
Furosemide (mg / kg)	1.5 (0.8-2.5)	1.6 (0.1-12)	0.391

Table 3: The relationship between postoperative data and delayed graft function.

	DGF (+) n=43	DGF(-) n=163	*P*-value
Postoperative Hemoglobin, mg / dl	7.7 (5-11)	8.4 (6.1-13)	0.359
Postoperative Hypotension%	16.3	18.4	0.473
Postoperative Hypertension%	69.8	65	0.535
Erythrocyte Suspension%	53.5	21.5	0.01
Fresh Frozen Plasma%	48.8	8.6	0.01
Mortality%	9	2.5	0.061
Graft loss%	27.9	2.5	0.001
Hospital stay, days	13(5-30)	11(4-34)	0.768

Discussion

DGF remains a significant complication after renal transplantation. In this retrospective study, the variables of renal transplantation process performed at our center and subsequent risk factors for DGF, and associated complications were examined.

In our study, 43 (20.9%) patients had DGF. In the literature, the rate varies widely between 2% and 50% [5]. In a study of 86,682 patients who underwent renal transplantation, the DGF rate was 21%, similar to our study [6] .

A crucial factor leading to DGF appears to be hypoperfusion-related cell damage, besides immunological factors. This process is further exacerbated by ischemia-reperfusion injury [7]. According to several studies focusing on DGF, donor-related risk factors include age, comorbidity, BMI, and final creatinine level, recipient-related risk factors include age, BMI, comorbidity, and race, and procedure-related risk factors include cold ischemia time and surgical duration [8, 9].

DGF rate is approximately 25% after cadaveric and 1%–8% after living-donor renal transplantations [10, 11]. The cadaveric donor transplantation procedure involves almost all risk factors for DGF (long cold ischemia time, ischemia-reperfusion injury, and donor-related comorbidities) [12]. In our study, DGF was significantly higher in the cadaveric group.

Lauronen et al. [13] evaluated 846 patients who underwent renal transplantation and reported that the cold ischemia time and DGF rate were significantly correlated. The mean cold ischemia time was 1,080 min in this study. A general opinion is that the cold ischemia time should be <12 h. [13-15]. In our study, the overall mean cold ischemia time was 450 (60–1.200) min, and there was a significant correlation between cold ischemia time and DGF. The cold ischemia time varied significantly between the living and cadaveric donor groups. However, when these two groups were evaluated separately for DGF and cold ischemia time, no significant correlation was observed between the two. The short cold ischemia times at our center compared with those reported in the literature can explain this.

HLA is considered an important biological barrier for successful transplantation [16]. However, modern immunosuppressive agents reduce the effect of HLA matching. In the revised UK Kidney Allocation Scheme, the HLA-A match is no longer required [17]. The European Renal Transplantation Guide still recommends HLA-A, HLA-B, and especially, HLA-DR matching as much as possible [18]. In a meta-analysis published by Shi et al., they emphasized that HLA mismatching is a prognostic factor, and in particular, HLA-DR matching is effective in graft survival [19]. The relationship between DGF and HLA subgroup and total matching was not shown in our study.

Diabetes mellitus increases ischemia-reperfusion injury due to chronic inflammatory process and increased oxidative stress [20]. Diabetes mellitus is mentioned in most studies as an independent risk factor for DGF [21, 22]. In addition, chronic renal insufficiency can cause significant changes in insulin metabolism and blood sugar regulation. According to the glomerular filtration rate, insulin clearance changes and hypoglycemia or hyperglycemic attacks may occur. In our study, similar to the literature, the presence of diabetes mellitus was identified as a facilitating factor for DGF.

Hemodynamic stability is very important in terms of graft perfusion, especially in the intra operative period [23]. Several factors such as anesthesia induction, anesthesia maintenance, proper fluid replacement, surgery duration, surgical technique (laparoscopic/open), and intra operative blood loss affect intra operative hemodynamics and organ perfusion. In our study, the patients were hemodynamically stable in the intra operative period; there was no significant difference between the DGF and non-DGF groups in terms of blood and blood product transfusion and fluid replacement. As the laparoscopic technique causes less blood loss, has shorter surgical duration and leads to more stable hemodynamics, it stands out in renal transplantation [24]. Although the number of patients was not evenly distributed (laparoscopic:14; open: 192), the DGF rate was lower in the open surgery group in our study. There was no difference between the two groups in terms of surgery duration, blood and blood product transfusion, and hemodynamic instability. Renal perfusion associated with increased intra-abdominal pressure during laparoscopic technique was a subject requiring further investigation.

Hypoperfusion, which is responsible for possible complications after transplantation, develops after insufficient oxygen delivery. Unless the concentration of hemoglobin, which is an important component of oxygen delivery, falls under the threshold (7 g/dl if there is no acute coronary syndrome), erythrocyte transfusion is not recommended, especially in intensive care patients, because of its possible side effects [25-

27]. In particular, multiple blood and blood product transfusions affect immunization through HLA, resulting in adverse effects such as acute graft rejection after transplantation [28]. In our study, hemoglobin levels were similar in patients with and without DGF in the first postoperative week. However, these similar hemoglobin levels were significant in patients with DGF receiving erythrocyte suspension and freshly frozen plasma.

DGF indicates hypoperfusion of not only the kidney but also the whole body. An increased mortality rate is expected in cases of hypoperfusion, ischemia-reperfusion injury, and possible comorbidities in patients with renal failure who require treatment regimens, such as immunosuppressive therapy, which have severe side effects [29]. Using hemodialysis for the treatment of patients with DGF may reduce early mortality rates. In our study, mortality rates in patients with DGF were similar. The duration of hospital stay was insignificantly higher in patients with DGF compared with those without. Graft loss rate was significantly higher in patients with DGF.

Limitations

This study has several limitations, the most prominent being its retrospective and single-center design. Donor data could not be evaluated due to the lack of recorded data on donors. Existing comorbidities and duration were interpreted in accordance with the data.

Conclusion

There are ongoing studies that focus on the risk factors and occurrence mechanism in DGF. Reducing DGF after renal transplantation may also decrease graft loss and mortality rates.

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