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# Risk factors for delayed graft function in deceased donor kidney transplantation; a potential preventive role for intraoperative thymoglobulin

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## ABSTRACT

**Introduction:** Delayed graft function (DGF) is associated with significant adverse outcomes in deceased donor kidney transplantation (KT) including lower graft survival. However, risk factors and potential preventive strategies like intraoperative rabbit antithymocyte globulin (rATG; thymoglobulin) have not yet been fully evaluated.

**Objectives:** The aim of this study was to investigate DGF risk factors and determine the association of intraoperative rATG with the risk of DGF in deceased donor kidney recipients.

**Patients and Methods:** We retrospectively examined medical records of 163 first time deceased donor kidney transplant recipients at two major kidney transplant centers from 2014 to 2016. All the donors were standard heart-beating, brain death donors. Risk factors for DGF in recipients were evaluated using multivariate logistic regression analysis.

**Results:** The mean recipients' age was 43±13 years and the majority of participants were male (64%). The overall rate of DGF was 27%. Intraoperative rATG was significantly associated with a lower rate of DGF (adjusted odds ratio [AOR], 0.33, 95% CI, 0.11-0.95). Intraoperative transfusion (AOR, 3.7, 95% CI, 1.4-9.9) and diabetes mellitus (AOR, 3.7, 95% CI, 1.5-8.9) were significantly associated with higher risk of DGF.

**Conclusion:** This study showed that intraoperative blood transfusion and diabetes mellitus were associated with increased risk of DGF. Meanwhile, administration of intraoperative rATG was associated with reduced odds ratio of DGF. Future studies are needed to evaluate the potential role of rATG in DGF-related renal outcomes.

### Implication for health policy/practice/research/medical education:

The aim of this study was to investigate DGF risk factors and determine the association of intraoperative rATG with the risk of DGF in deceased donor kidney recipients at our centers. This study showed that intraoperative rATG induction therapy was associated with decreased incidence of DGF in deceased donor kidney recipients. In addition, intraoperative blood transfusion and recipient diabetes were independent risk factors for DGF.

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## Introduction

In patients with end-stage renal disease (ESRD), kidney transplantation (KT) is the most desired modality for renal replacement therapy (1) given that it improves quality of life and is associated with a lower risk of

mortality compared to maintenance dialysis (2). However, KT is not without risks as renal allograft recipients may encounter various post-transplant complications such as rejection or delayed graft function (DGF), both of which can adversely impact graft and patient survival. DGF,

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usually defined as the need for dialysis within seven days following transplantation, is a well-known complication especially in deceased donor kidney recipients. While DGF has a lower incidence in living donor kidney recipients (3), its frequency in deceased donor kidney recipients varies widely from 5% to 50% (4, 5) due to several factors including differences in DGF definitions, administered induction immunosuppressive regimens, organ procurement techniques and many other factors that might affect the risks and incidence rate of DGF in different transplant centers (4). Other well-studied recipient related risk factors for DGF include male gender, high body mass index (BMI), previous transplant, diabetes, pre-transplant dialysis and its duration and need for pre-transplant transfusion (6). Regardless of underlying cause, DGF occurrence is associated with shorter graft survivals and higher acute cellular rejection episodes (6).

Rabbit antithymocyte globulin (rATG; thymoglobulin) is frequently used as an induction therapy agent in deceased donor KT especially in recipients with increased immunologic risk factors in order to reduce the risk of graft rejection and DGF (7-9). It is believed that thymoglobulin has several pharmacologic properties, some of which can help to control the inflammation associated with ischemia reperfusion injury and thus reduce the risk of pathogenesis of DGF (10).

### Objectives

The aim of this bi-center, historic cohort was to investigate DGF risk factors and to determine the association of intraoperative rATG with the risk of DGF in deceased donor kidney recipients at our centers.

### Patients and Methods

#### Study population

In this study, we reviewed medical records of all consecutive first time deceased donor kidney transplant recipients who were on maintenance dialysis from December 2014 to January 2016 in 2 medical centers in Tehran. All patients in both centers received maintenance immunosuppressive treatment including tacrolimus (adjusted dose to reach whole blood trough level of 8-12 ng/mL), mycophenolate mofetil (500 mg TID), and prednisolone. In center one the standard protocol required rATG (1 mg/kg) infusion in the operating room prior to incision for 6-8 hours and repeated daily for 3-4 days. In center two intra-operative rATG was not administered and it was standard protocol to infuse thymoglobulin (1 mg/kg for 4-7 days) only to patients with urine output <75 mL/h within the first 48 hours or failure of serum creatinine to decrease by 10% in the first 48 hours. All donors were standard heart beating, brain death donors. Unfortunately, due to retrospective nature of the study detailed information about donors and cold ischemic time was not available. We excluded patients with incomplete medical records and those with

preemptive KT.

### Definitions and variables

DGF was defined as the need for dialysis within the first week after KT. The cause of ESRD; duration of maintenance dialysis; the presence of DGE, intraoperative administration of thymoglobulin and total dose of rATG, operation duration, intraoperative transfusion, changes in systolic blood pressure after operation, duration of hospital stay, serum creatinine within the first 7 days after KT and at the time of hospital discharge, history of diabetes and hypertension, gender, weight, height and body mass index (BMI) of the patients were also recorded from patients' medical reports.

### Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consent was taken from the patients. The study protocol was approved by local ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1395.71). This study was a part of the thesis by Neda Naderi, supported by Tehran University of Medical Sciences (#9411402003).

### Statistical methods

Data were analyzed using SPSS (SPSS Inc., Chicago, IL, USA) version 16.0 software for descriptive statistics. Chi-square and student t test were used for categorical and continuous variables, respectively. We used STATA version 13.0 to calculate odds ratios and perform logistic regression analysis. A multivariate logistic regression model was used to investigate associations between DGF and putative risk factors. To evaluate the association between demographic and clinical variables with DGF we first used univariate regression analysis. Variables with a *P* value of less than 0.2 or those that to our previous knowledge could be associated with DGF were chosen. These variables were included in multivariate logistic regression. Variance inflation factor (VIF) was used to quantify the severity of multicollinearity and from variables with high collinearity one was included in the final regression model. Also, *P* value of less than 0.05 was considered statistically significant.

### Results

#### Patient population

Medical records of 234 deceased donor kidney recipients were reviewed. Seventy-one patients did not fulfill inclusion criteria (19 preemptive transplantation and 52 incomplete medical records). A total of 163 patients were included in the study. The median age of the patients was 44 years (11-73 years) and 63.8% (104) were male (Table 1). Thirty-six (22.1%) patients experienced a more than 20 mm Hg drop in systolic blood pressure and 27 (16.6%) received packed RBC during surgery. History of diabetes

**Table 1.** Demographic and clinical characteristics of kidney recipients

Variable		
Sex	Male	104 (63.8%)
	Female	59 (36.2%)
Age (y)		43.80±13.48 (11-73)
Age of patient ≥65 years	No	157 (96.3%)
	Yes	6 (3.7%)
BMI (kg/m <sup>2</sup> )		23.94 ± 3.86 (15.52-33.08)
BMI ≥ 30	No	149 (91.4%)
	Yes	14 (8.6%)
Duration of dialysis before kidney transplantation (mon)		26.55±25.93 (1-156)
History of diabetes	No	118 (72.4%)
	Yes	45 (27.6%)
Operation duration (h)		3.35±0.88 (1.5-6.0)
ATG received on operation day	No	74 (45.4%)
	Yes	89 (54.6%)
ATG total dose (mg/kg)		3.75±2.55 (0-8.57)
DGF	No	119 (73.0%)
	Yes	44 (27.0%)
>20 mm Hg drop in systolic blood pressure after operation	No	127 (77.9%)
	Yes	36 (22.1%)
Packed RBC transfusion during surgery	No	136 (83.4%)
	Yes	27 (16.6%)
Hospitalization duration (days)		16.99±10.54 (7-90)
Serum creatinine at discharge (mg/dL)		1.70±1.05 (0.6-11.3)

Data has been presented as number (percent) or mean± standard deviation (min-max).

BMI: Body mass index; DGF: Delayed graft function; RBC; Red blood cells.

mellitus was positive in 45 (27.6%) cases and the duration of dialysis before KT was 26.55 ± 25.93 months (1-156 months).

Eighty-nine patients from center one and seventy-four patients from center two were included in the study. Age, duration of dialysis prior to kidney transplant, duration of surgery, history of diabetes mellitus and BMI were significantly different in these two centers (Table 2). There was no statistically significant difference in other studied variables between the centers (Table 2).

### Delayed graft function

The rate of DGF in kidney transplant recipients was 27.0% (44/163). Unadjusted data showed that positive history for DM was observed in 50% (22/44) of DGF cases which was statistically significant ( $P < 0.001$ ). Transfusion during operation and BMI  $>30$  kg/m<sup>2</sup> were significantly more common in DGF positive patients (22.9.5% versus 11.8%,  $P = 0.007$ ; 15.9% versus 5.9%,  $P = 0.043$ , respectively). Mean serum creatinine concentration at the time of hospital discharge and length of hospital stay was significantly higher among patients with DGF compared to those without DGF (2.5 versus 1.4 mg/dL and 25

versus 14 days, respectively). There was no statistically significant difference between age, sex, duration of dialysis, administration of rATG, BMI and history of hypertension between two groups (Table 3).

Our final regression model included age, gender, duration of dialysis, duration of transplant surgery, intraoperative administration of rATG, BMI, history of diabetes mellitus, more than 20 mm Hg drop in blood pressure after operation, and transfusion during surgery (Table 3). Intraoperative rATG administration was significantly associated with a lower rate of DGF (adjusted odds ratio [AOR], 0.33, 95% CI, 0.11-0.95). The need for intraoperative blood transfusion (AOR, 3.7, 95% CI, 1.4-9.9) and presence of diabetes mellitus in transplant recipients (AOR, 3.7, 95% CI, 1.5-8.9) were significantly associated with higher risk of DGF. There was no statistically significant association between DGF and recipients' age, gender, BMI or duration of pre-transplant dialysis (Table 3, Figure 1). The odds ratio for developing DGF was higher in patients with longer operation time but was not considered statistically significant (AOR, 1.73, 95% CI, 0.98-3.04,  $P = 0.058$ ). Age, gender, duration of dialysis before transplant, more than 20 mmHg drop in blood pressure after operation and BMI were not associated with increased risk of developing DGF.

### Discussion

In this retrospective cohort study of 163 first time kidney transplant recipients we found that intraoperative rATG administration was associated with a decreased risk of DGF after adjustments for age, sex, BMI, duration of dialysis, history of diabetes mellitus,  $>20$  mm Hg drop in systolic blood pressure, operation duration and intraoperative transfusion. Conversely, we identified that history of diabetes mellitus and need for intraoperative blood transfusion were associated with an increased risk of DGF that remained robust after adjustment for above variables.

The incidence of DGF has increased over time in concordance with the use of high-risk kidneys from expanded criteria donors and donation after cardiac death (11-13). Several modalities have been investigated in both deceased donors and recipients to attenuate the risk of DGF (14-16), such as using vasodilators, antioxidant agents, and different types of immunosuppressive induction (11). Currently, rATG, a lymphocyte-depleting polyclonal antibody, and basiliximab, an interleukin-2 receptor monoclonal antibody, are the most commonly used biologic agents for immunosuppressive induction therapy in kidney transplant (17,18). Although the main purpose of the induction therapy is to lower the incidence of acute rejection, some reports surmised an additional role for rATG to reduce the rate of DGF by suppressing the alloimmunity and ischemia reperfusion injury (19, 20). There are several mechanisms by which

**Table 2.** Demographic and clinical characteristics of kidney recipients according to intraoperative administration of rATG (centers 1 and 2)

	ATG received on operation day		P
	Yes (n = 89, center 1)	No (n = 74, center 2)	
Age	41.3±13.29	46.7±13.19	0.011
Duration of dialysis (mon)	31.3±29.29	20.9±19.95	0.010
Operation duration (h)	3.85±0.64	2.74±74	0.001
Serum creatinine at discharge	1.62±1.28	1.79±0.65	0.285
Hospitalization duration (days)	16.7±12.70	17.3±7.20	0.727
ATG dose (mg/kg)	4.96±1.26	5.28±1.91 (n=32)*	<0.001
BMI	23.6±3.45	24.3±2.29	0.217
Gender (male)	53 (59.6%)	51 (68.9%)	0.215
History of Diabetes (positive)	19 (21.3%)	26 (35.1%)	0.050
>20 mm Hg drop in systolic BP	17 (19.1%)	19 (25.7%)	0.314
Transfusion during surgery	18 (20.2%)	5 (6.8%)	0.168
Age of patient equal or more than 65	1 (1.1%)	9 (12.2%)	0.057
BMI ≥30	4 (4.5%)	10 (13.5%)	0.041
History of hypertension	62 (69.7%)	53 (71.6%)	0.785

\*rATG was administered after surgery in those patients with urine output <75 mL/h within the first 48 hours or failure of serum creatinine to decrease by 10% in the first 48 hours.

Data has been presented as number (percent) or mean± standard deviation.

BMI; Body mass index; DGF: Delayed graft function; RBC; Red blood cells

**Table 3.** Factors associated with delayed graft function in kidney recipient patients

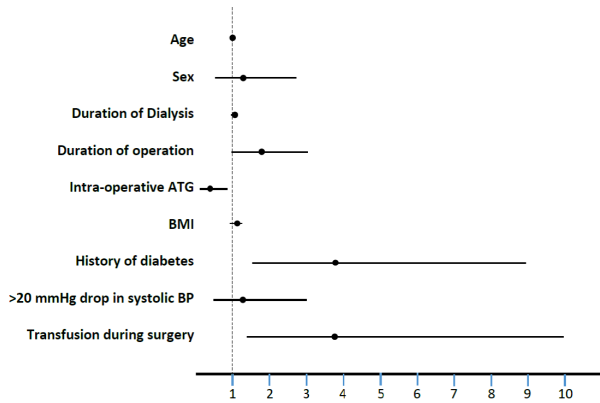
	Delayed graft function		P value	Unadjusted OR (95% CI)	Adjusted OR(95% CI)
	No (119)	Yes (44)			
Age (y)	43.1±13.72	45.5±12.80	0.342	1.01 (0.99-1.04)	0.98 (0.95-1.02)
Sex (male)	77 (67.7%)	27 (61.4%)	0.693	1.15 (0.56-2.35)	1.22 (0.55-2.74)
Height (cm)	167.3±11.29	167.1±9.04	0.914		
Weight (kg)	66.6±13.59	69.7±14.28	0.274		
Duration of dialysis (mon)	27.3±27.06	24.4±22.73	0.527	0.99 (0.98-1.01)	0.99 (0.98-1.01)
Operation duration (h)	3.32±0.84	3.42±1.00	0.513	1.14 (0.77-1.69)	1.73 (0.98-3.04)
Serum creatinine at discharge (mg/dL)	1.40±0.39	2.5±1.68	<0.001		
Hospitalization duration (days)	14.0±5.78	24.9±15.45	<0.001		
ATG received on operation day	69 (57.0%)	20 (45.4%)	0.154	0.60 (0.30-1.21)	0.33 (0.11-0.95)
ATG total dose (mg/kg)	3.15±2.55	5.36±1.71	<0.001		
BMI, kg/m <sup>2</sup>	23.7±3.76	24.7±4.08	0.145	1.07 (0.98-1.17)	1.06 (0.95-1.18)
History of diabetes mellitus (positive)	23 (19.3%)	22 (50%)	<0.001	4.17 (1.98-8.80)	3.72 (1.55-8.95)
>20 mm Hg drop in Systolic BP	24 (20.2%)	12 (27.3%)	0.332	1.48 (0.67-3.30)	1.21 (0.49-3.02)
Transfusion during surgery	14 (11.8%)	13 (29.5%)	0.007	3.14 (1.34-7.39)	3.70 (1.38-9.94)
Age of patient ≥65	5 (4.2%)	1 (2.3%)	0.561		
BMI ≥30 kg/m <sup>2</sup>	7 (5.9%)	7 (15.9%)	0.043		
History of hypertension	81 (68.1%)	34 (77.3%)	0.252		

Data has been presented as number (percent) or mean± standard deviation (min-max).

BMI; Body mass index, BP, blood pressure; ATG, antithymocyte globulin; OR, odds ratio.

rATG may exert protective effects in the prevention of DGF. For instance, rATG therapy may be associated with amelioration of some of the mechanisms which underlie ischemia reperfusion injury (21, 22). In this regard, rATG therapy can exert its effects through blockade of adhesion molecules, reducing the surface expression of  $\beta_2$  integrin and importantly inducing T lymphocyte depletion. The presence of CD<sub>4</sub> and CD<sub>8</sub> T cells at the time of reperfusion may be associated with increased risk of reperfusion injury and DGF (19,23). The clinical impact of rATG has been evaluated in several studies which have shown

that rATG as an induction therapy can be beneficial in deceased donor kidney transplant recipients with DGF (24-26). Goggins et al evaluated intraoperative and postoperative administration of rATG in deceased donor kidney transplant recipients in a prospective randomized study. They found that intraoperative thymoglobulin was associated with a significant decrease in DGF occurrence, better graft function within the first month post-transplantation and shorter hospital stay (27). Recently, the effects of rATG as an induction immunosuppressive agent was studied in kidney transplant patients who received



**Figure 1.** Adjusted odds ratios and confidence intervals for development of DGF in the final multivariate regression model.

the allograft from donors after brain death followed by circulatory death. The results showed that rATG induction therapy was associated with lower incidence of DGF (28). Furthermore, a recent investigation by Lee et al also revealed that even in low immunologic risk recipients, the incidence of biopsy-proven acute rejection was lower with thymoglobulin compared with basiliximab (29).

However, it should also be noted that there are also studies which compared the effects of rATG with newer antibody induction regimens (19,30,31). In a randomized controlled trial, Brennan et al indicated that rATG induction therapy was superior to basiliximab in preventing acute rejection episodes. However, there was no significant difference between the two groups regarding the incidence of DGF (30). A meta-analysis of randomized controlled trials was conducted by Zheng et al on efficacy and safety of rATG and alemtuzumab as induction therapy in kidney transplant recipients. The findings of this study demonstrated that there were no significant differences between alemtuzumab and rATG for biopsy-proven acute rejection, mortality, graft failure and DGF (31). In light of the discrepancy between the available studies on the role of rATG in the prevention of DGF, future studies will need to further the potential utility of this therapy for this condition.

Numerous factors in donors and recipients have been found to be associated with a greater risk of DGF development. In the recipients, male gender, older age, higher BMI, comorbid diabetes mellitus and longer pre-transplant dialysis duration have been associated with DGF (6,32-34). In the present study, we did not find any significant association between DGF and recipients' gender, age, BMI or pre-transplant dialysis duration. This discrepancy might be related to small sample size of our study.

The observed effect of pre-transplant transfusion on allograft survival has changed during recent decades. In earlier studies, it had been suggested that pre-transplant blood transfusion in deceased donor kidney transplant

recipients, improved allograft survival due to increasing immune tolerance (35,36). In contrast, a systematic review of 180 studies in 2013 showed that pre-transplant blood transfusion was a major cause of allosensitization and consequently was correlated with enhanced risk of rejection and graft loss (37). A recent investigation by Mazzeffi et al examined the effect of intraoperative blood transfusion on renal allograft outcomes. The results of this study showed that intraoperative blood transfusion not only increased the risk of DGF but also increased the incidence of post-operative sepsis (38). In accordance with the study by Mazzeffi et al, we showed the role of intraoperative blood transfusion as a risk factor for DGF.

It has been shown that renal transplant recipients who are diabetic are at increased risk for development of DGF (32,39,40). During a retrospective study, Bzoma et al assessed the clinical consequences of recipients' diabetes on the transplant outcomes of paired kidneys in diabetic and non-diabetic patients who received kidney grafts from the same donor. The result of the study showed that diabetic patients were exposed to more events of DGF (40). This finding is in agreement with our study that identified diabetes as a strong risk factor for DGF. Diabetes potentiates the severity of the ischemic reperfusion injury through chronic inflammation and oxidative stress. Additionally, hyperglycemia as a result of corticosteroid bolus at the time of ischemia reperfusion can accentuate oxidative stress and renal injury(41). In addition, perioperative cardiac events and hemodynamic instability predispose diabetic recipients to the development of DGF (42).

### Conclusion

Our study showed that intraoperative rATG induction therapy was associated with decreased incidence of DGF. Additionally, the need for intraoperative transfusion and recipient diabetes were risk factors for DGF. These findings will need to be further evaluated in larger randomized clinical trials.

### Study limitations

Several limitations of our study need to be mentioned. Firstly, the present study is retrospective in nature; therefore, a causal relationship cannot be inferred. Another limitation of the current study is the small sample size and the homogeneity of the patient population (all of the patients were from the Middle East) which limit its generalization to more heterogeneous patient populations. In addition, there were recipient, donor and graft related confounders that we could not evaluate their effects on DGF occurrence due to insufficient data collection.

### Authors' contribution

NN participated in study design, data collection, manuscript preparation, and editing. AA participated in manuscript preparation and editing. MRK, SDK and MLP

joined in concept, design and editing. HM contributed to manuscript preparation and editing. MHS contributed to study design, data analysis, manuscript preparation and editing. AS and AM joined in study design and data collection.

### Conflicts of interest

All authors declare no conflicts of interest.

### Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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