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Kidney Transplantation: Local Donor and Distant Recipient, Is It Feasible? A Retrospective Cross-Sectional Study

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Abstract

Background: Delayed graft function (DGF) and slow graft function (SGF) are complications after kidney transplantation that resulted in poor short-term outcome.
Objectives: In this study, we evaluate a new model for deceased kidney transplantation to reduce the cold ischemia time and its effect on DGF and SGF as short-term outcomes.
Methods: We have included 814 deceased kidney transplanted patients in this study. All of the donors were local, while the recipients were both local and nonlocal. Kidney recipient's outcomes (included mortality rate as well as DGF and SGF), age, gender, BMI, blood group, Rh, allograft renal function, transplantation date, kidney transplantation history, PPD, positive history of rheumatologic disorders, the distance between home of recipient and the transplantation center, cardiovascular disease, and dialysis duration was evaluated for all patients.
Results: The incidence of DGF and SGF were 24.8% and 20.5%, respectively. There were no statistical differences in the rate of DGF and SGF between local and distant recipients ($P > 0.21$). The rate of DGF was significantly higher in females as well as 40 - 65 year old recipients ($P < 0.05$). In logistic regression multivariate analysis, DGF and SGF were significantly correlated with BMI, blood group, the history of kidney transplantation, and dialysis duration.
Conclusions: This study showed the feasibility of using a local donor for a distant recipient as well as reduction of cold ischemia time and lower rate of DGF. It is obvious that the shorter CIT, which resulted from usage of local donor, can lead to better kidney transplant outcomes.

Keywords: Kidney Transplant, DGF, SGF, Deceased, Cold Ischemia Time, Distance Recipient

1. Background

Kidney transplantation and dialysis are the treatments for end stage renal disease (ESRD) patients. Although kidney transplantation is the best treatment for ESRD patients, a significant portion of ESRD patients could not achieve to a functional graft as a treatment, therefore, they will be under dialyzing patients (1, 2).

The vast majority of physicians prefer kidney transplantation in patients who don't have any contraindication for it. This preference is due to a longer survival (eight to 20 years), higher quality of life, lower incidence of anemia, bone disease, and cardiovascular as well as neurological events in transplanted patients versus under-dialyzing patients (3, 4).

There are two models for kidney transplantation: (1) living kidney transplantation and (2) deceased kidney transplantation. For the first model, there is a living kidney transplant donor who donates one of his or her kidneys to and ESRD patient (5, 6). Furthermore, for the second model, there is a deceased donor where his or her kidney donates will be donated (7).

Previous studies showed the better short and long term outcomes with living kidney transplantation in comparison to deceased kidney transplantation (1, 8, 9).

Several reasons that have been cited for better outcomes of living kidney transplantation, which includes short cold ischemia time (CIT) and more preparation time before surgery in living kidney transplantation, high levels of the serum inflammatory markers in deceased kid-

ney transplantation, more human leukocyte antigen (HLA) compatibility of the living related patients, and etc. (10-13).

Although living kidney transplantation is the first choice for an ESRD patient, deceased kidney transplantation has a better outcome than dialysis. Therefore, nowadays deceased kidney transplantation has a significant contribution in kidney transplantation (14, 15).

One of the theories for improving the results of the deceased kidney transplant, which we believe in, is that "when we call the recipient to the transplantation center, even if the recipient is distance, we will get better results than when we send the graft to the recipient's place of life".

2. Objectives

In this theory, it is assumed that if we bring patients from far distances to the center of where the kidney donor is located to receive a deceased kidney transplant, short-term outcomes do not differ significantly from using local recipients.

This study intends to examine the operational results of this theory as a new model of allocation, which can improve deceased kidney transplantation results as well as evaluate the feasibility of this model.

3. Methods

3.1. Study Design

We conducted a retrospective cross-sectional study to evaluate the renal allograft function as well as its impact on a short-term outcome among 814 deceased kidney transplants performed in Baqiyatallah Transplant Center between August 2003 and June 2016, Tehran, I.R. Iran. This study was approved by the local Ethics Committee of Baqiyatallah University of Medical Sciences as the ethical standards of the Declaration of Helsinki confirmed.

3.2. Study Subjects

In the current study, we included all donors who were from Tehran (local donors) as well as enrolled both local and distant recipients. Pediatric and adult transplant patients as well as first, second, or third kidney transplants were included in this study.

Patients who received a kidney from a living donor and recipients with incomplete data were excluded from the study.

3.3. Definitions

The primary outcome of this study was to determine the short term renal allograft outcome at the time of discharge, while the secondary outcomes were defined delayed graft function (DGF), slow graft function (SGF), and immediate graft function (IGF) in deceased kidney recipients (16, 17).

DGF was defined as dialysis requirements during the first postoperative week while acute rejection, vascular renal allograft complications, and urinary tract obstruction were excluded.

SGF was defined as a serum creatinine above 3.0 mg/dL without the need for dialysis after five days of kidney transplantation.

IGF was defined as a serum creatinine lower than 3.0 mg/dL on day five, immediately after kidney transplantation.

Pediatric transplant recipient was considered as a patient who was $\leq$ 18 years old and an adult transplant recipient was considered as patient who was above 18 years of age.

In addition, pre-emptive kidney transplantation was defined as a transplantation done prior to initiation of maintenance dialysis (18).

3.4. Data Collection

The clinical and biochemical data recorded for all patients were patient's status (being alive or deceased), age, gender, BMI, blood group, Rh, allograft renal function, transplantation date, kidney transplantation history, PPD, Rheumatologic-Lupus positive history, the distance between home of recipient and the transplantation center, cardiovascular disease, and dialysis duration.

All of the donors were local (located in Tehran), however, there was no limitation in the distance of the recipients.

3.5. Immunosuppressive Protocols

The immunosuppressive protocol for all of the patients was based on calcineurin inhibitors (cyclosporine/tacrolimus), mycophenolate, and prednisolone. In our center, calcineurin inhibitors doses given to kidney recipients were administered upon its trough levels. Induction therapy using anti-thymocyte globulin (ATG) was preserved in patients who were highly sensitized patients or in most recipients who had DGF.

3.6. Statistical Analysis

Data were analyzed using the computer software program SPSS version 23.0 for Windows (IBM Inc., Somers, NY, USA). Qualitative variables were expressed as number and

percentage, while quantitative variables were shown by mean ± standard deviation (SD). Quantitative and qualitative variables were compared by Student *t*-test and chi-square, Fisher exact test, and ANOVA as univariate analyses. Multivariate logistic regression backward model was used for DGF. A P value less than 0.05 was considered as a statistically significant level and 95% confidence interval was also considered to be a reliable estimate. We used P value less than 0.2 for entering variables into the multivariate regression model (Table 1).

4. Results

4.1. Subjects

Of the 814 deceased kidney transplants, eight (1%) cases died after the surgery due to pulmonary thromboembolic accident, sepsis, or myocardial infarction. The rate of kidney transplantation in terms of age included 18 (2.2%) pediatric recipients (2.2%) cases, while 796 (97.8%) were adult transplants. In addition, 246 of the recipients (30.2%) came from a local region and 568 (69.8%) of patients came from distant regions. The mean cold ischemic time for the patients was 190 ± 50 minutes.

The mean age of recipients was 46±14 years old. The majority of patients were male (61% vs. 39%). All subjects received the first or second kidney from a deceased donor.

4.2. The Rate of Incidence DGF

In the current study, the incidence of DGF and SGF were low (n = 202 and 167; 24.8% and 20.5%, respectively) and 54.7% (n = 445) of them had IGF.

4.3. The Risk Factors of DGF

The rate of DGF was significantly higher in females (P < 0.002), while there was no statistical difference in SGF between both genders (P = 0.2) (Table 2). The risk factors for DGF and SGF in univariate analysis were female gender (P = 0.01), age (P = 0.02), kidney transplantation history (P = 0.005), and positive PPD (P = 0.031) (Table 2). Patients who were 40 - 65 years old had the highest rate of DGF and SGF (27.4% and 23%, respectively).

Furthermore, in logistic regression multivariate analysis, DGF and SGF were significantly related with BMI, blood group, the history of kidney transplantation, and dialysis duration. The risk of the DGF and SGF increased with BMI increase. Moreover, the risk of DGF and SGF in the AB blood group was double versus the A, B, and O blood group. In addition, the patients who had a previous kidney transplantation have a higher risk of DGF and SGF.

4.4. The Short Term Outcome

The early mortality rate, after transplantation before discharge of hospital, was approximately 1% (eight cases).

5. Discussion

The current study introduced a novel strategy in selection of the only regional deceased kidney donors for local or distance recipients in terms of decreasing the graft cold ischemia time and its complications such as DGF. Previous studies have reported that this protocol reduces CIT (190 ± 50 minutes) (19). In previous studies, the correlation between CIT and increased risk of undesirable secondary outcome (such as DGF) have been proven. Simpkins et al. evaluated 38467 kidney transplant patients and revealed that the patients who received a kidney with prolonged CIT had a higher incidence of DGF after the kidney transplant (20). Furthermore, Salahudeen et al. found the better short- and long-term outcomes in grafts with less than 20 hours of CIT in comparison to those had more than 30 hours of CIT. In addition, they reported that significant graft loss was seen in recipients with prolonged CIT (21). In parallel, in another study by Salazar Meira et al. the role of the distance in the kidney transplantation has been investigated and their study suggested the higher rate of DGF and CIT in patients who received a graft from deceased kidney donors of more than 100 km away (22). Therefore, the prolonged CIT is one of the problems in the quality of the grafts in the deceased kidney transplantation.

Previous studies reported fairly high CIT in some current allocation systems; for example, CIT reported from United States, Turkey, and Tunisia, 21 ± 7, 14, and 18 to 23 hours, respectively (23-25).

Therefore, using local deceased kidney donors for deceased kidney transplantation could be one of the ways to reduce CIT and increase the cadaveric transplantation outcome.

5.1. Delayed Graft Function and Slow Graft Function

In our findings, the frequency of DGF was 24.8% (Table 2); no significant differences were found in the rate of DGF in local recipients and non-local recipients (P value > 0.05) (Table 2). Interestingly, the rate of DGF in our center for deceased grafts was low while there was no available HLA matching protocol in the procurement of Iran (26). One of the strong reasons of this difference could be the lower CIT, which is about one-third of the kidney allocation system (KAS) in the United States (27).

Some studies have reported that the frequency of DGF in deceased and living kidney transplantation were around 50% and 4% - 10%, respectively; a lower rate of DGF

Table 1. Multivariate Logistic Regression Analysis for the Risk of DGF and SGF

	95% CI for EXP(B)			
	OR	Lower	Upper	P Value
BMI	1.073	1.013	1.136	0.016
ABO blood group				
A	0.855	0.450	1.626	0.633
AB	2.367	1.014	5.523	0.046
B	1.154	0.589	2.261	0.675
O	1		Based category	
Kidney transplantation				
Positive	3.386	1.504	7.621	0.003
Negative	1		Based category	
Dialysis duration, y				
0 - 1	1		Based category	
1 - 2	0.980	0.532	1.805	0.948
> 2	0.530	0.284	0.986	0.045
Gender				
Male	0.651	0.387	1.097	0.107
Female	1		Based category	

Abbreviations: BMI, body mass index; DGF, delay graft function; SGF, slow graft function.

in living transplantation related to the shorter CIT (28, 29). In Turkey, DGF has reported 54.8% to 57.8% in deceased kidney transplants (25, 30). Nevertheless, there were few definite information regarding the frequency of DGF in other Middle Eastern countries. Moreover, the rate of DGF in Brazil and United States were 55.3% and 24.3%, respectively (22, 31).

One of the reasons for the similarities between our center and for example United States DGF, despite the lack of HLA typing in our center, is that we have lower CIT, as the previous studies have proven (19). It means that although CIT in the United States is higher than our study, we see a low DGF rate in the USA because of the high degree of matching. Therefore, it is anticipated that if we run the proposed model of using the local donor for all recipients along with maximum HLA matching, it can surprisingly improve the results of the renal transplantation.

It seems that one of the main reasons for this significant difference in frequency of DGF between deceased and living kidney transplants was related to lower CIT in living kidney recipients when compared to deceased kidney transplants (31). As Fattahi et al. reported, the mean CIT in our center was significantly lower than other studies (19, 24, 25).

One of the causes of the lower DGF occurrence in our deceased kidney transplants could be our graft providing system. In the majority of the kidney transplant centers in our country, there were only a few facilities for air transport of grafts in comparison to European and North American countries. Thus, except for special cases, regional allocation was considered for most centers in Iran. Therefore, CIT in our transplant patients were lower than other countries (19).

In addition, the rate of slow graft function (SGF) was also low, which was compatible with other studies that reported that the incidence of SGF was 20% - 30% (32, 33). Moreover, our findings regarding DGF and SGF was compatible with the previous studies in Iran, which evaluated the short-term outcome of the kidney transplantation (19, 34, 35).

5.2. Cold Ischemia Time in Our Study

CIT is one of the most impressive items in the fate of a graft in the deceased kidney transplantation.

In Iran, the graft providing unit of Masih Daneshvari Hospital is responsible for planning the allocation of kidney transplants. Unfortunately, there is no citation report on the amount of CIT in past researches. In our study, one of the important limitations is the lack of access to the CIT of the patients under study. Unfortunately, due to the collection of information from the files in the link center and

the lack of insertion of CIT in these cases, we could not enter this item in this study. In addition, due to the fact that we were collecting information from the files in the Baqiyatallah data center and the CIT information was not available in these cases, we could not enter this item in this study.

Fortunately, in the previous study that was conducted at the same center with the collaboration of the graft providing unit of Masih Daneshvari Hospital, the CIT was examined and 121 transplant recipients from deceased donors were examined; the CIT in that study for deceased kidney transplantation was 190 $\pm$ 50 minutes (19). Considering that all recipients, whether local or non-local, are called to our center for kidney transplantation, when they arrive at the center of the transplant process it is expected that there is no significant difference between the CITs of the local and non-local groups, however, it seems to be a study to investigate the matter needs to be done. Therefore, our study can be precondition for future studies that explore CIT in different local and non-local groups in this allocation model.

5.3. Distance of the Recipients and Feasibility of Transplantation Center

In this study, we called recipients from local areas or patients from further distances to our center. For each potential donor, we called 4 - 5 potential recipient, which were all on the waiting list. In this list, there are both local and non-local recipients. The potential recipients were prioritized from one to four-five by some factors, such as emergency state, age, antigen matching, and etc. This model does not cause any delay in transplantation process due to the fact that if the previous non-local potential recipient fails to bring himself to the hospital, there is a local potential recipient for the graft, which can be placed in the next priority. In this study recipients were divided into four groups: Local recipients, non-local patients with less than 150 km, 150 - 500 km, and more than 500 km. The rate of DGF in groups were: 26%, 27%, 24%, and 27.1% in local, $<$ 150 km, 150 - 500 km and $>$ 500 km groups, respectively. Interestingly, no relationship between the distance of recipients and transplantation outcome of the transplantation was seen (Table 1). Therefore, this results showed the fact that distance of the potential recipients was not a significant factor in the secondary outcome of deceased kidney transplantation.

5.4. Role of HLA Typing in Iran and Our Center

There are many criteria for finding the maximum matched recipients before allocation. One of the main laboratory tests is HLA typing, which influences the outcomes of the kidney transplantations (12, 36, 37). The previous researches described the HLA matching as a protective lab test to reduce the rate of the rejection, acute tubular necrosis, and DGF (34, 38, 39).

Nowadays, the majority of the reliable allocation systems accommodated the HLA typing in the donor-recipient matching (40-43). In Iran, donor-recipient matching includes solely the blood group, cross match, and panel reactive antibody (PRA). Unfortunately, HLA typing is not common before the first transplantation in our matching system (26). This could be one of the factors that decrease the outcome of the deceased transplantation and increase the rate of the DGF (34).

However, the rate of the DGF in this study was low (Table 1). Therefore, it seems that the reduced CIT was one of the most important factors impacted on the rate of DGF in our allocation system.

5.5. Proposed Model of Kidney Transplantation Allocation

This study showed the feasibility of the recipient calling to the transplantation center. It could be one of the main process that results in improved transplantation outcome by reducing CIT and the rate of DGF. In this model, in the center where the brain death donor is ready for operation, HLA antigen test will be done. After matching, the most matched recipient in the country makes a call to the center where the donor is located. In this strategy, there is no air transfer for graft and the time interval between the renal artery clamping in donor and graft reperfusion in recipient can be significantly reduced.

On the other hand, the distance of the patients could be one of the more challenging issues such that fatigue and the effects of the long distance may impress the kidney transplantation outcome. However, we evaluated this issue and achieved the non-significant difference between local recipient and long-distance recipients. Therefore, the distance of the recipient to the donor transplantation center could not be a worrying factor in the kidney transplantation.

In addition, the social support of the recipients (such as family of patients) could be reduced by this model. This reduction in family support is due to time restriction and force majority of the kidney transplantation. Therefore, to reduce this problem, a strong support is needed by the medical team such as psychologist, nurse, social workers, and etc. which is going on in our center it seems that cannot cause a significant problem in the transplantation outcome and could be covered by the higher quality outcomes of the deceased kidney transplantation in the CKD patients in long term (44). However, it is one of the disadvantages of this model.

5.6. Limitations

In this cohort retrospective study, we did not look at the long term outcomes of the patients and graft status. The CIT was not available as the distance divided, therefore, we reported the average CIT based on our previous research. As a result of the retrospective aspect, it may be having selection bias and information bias. In addition, when collecting the data, the 2017 transplantation data was not accessible; furthermore, there was also incomplete data, which were excluded from the study. On the other hand, the large sample size in our work is an advantage of this study.

5.7. Conclusion

This study showed the feasibility of the distant recipient calling the transplantation center where the donor located. Thus, this method was accompanied with reduction in CIT and low DGF. It is obvious that the shorter CIT resulted from usage of local donor can lead to better kidney transplant outcomes.

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Footnotes

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Table 2. Univariate Analysis of the Risk Factors in DGF, IGF, and SGF Patients[a]

Variable	DGF	SGF	IGF	Total	P Value
Gender					0.012
Male	106 (21.2)	107 (21.4)	286 (57.3)	499 (100)	
Female	96 (30.5)	59 (18.7)	160 (50.8)	315 (100)	
Mean ± SD	47 ± 13	48 ± 12	44 ± 14	46 ± 14	
Age, y					0.025
< 18	3 (16.7)	3 (16.7)	12 (66.7)	18 (100)	
18 - 40	56 (21.4)	41 (15.6)	165 (63.0)	262 (100)	
40 - 65	129 (27.4)	108 (23.0)	233 (49.6)	470 (100)	
> 65	11 (19.6)	12 (21.4)	33 (58.9)	56 (100)	
Mean ± SD	208 ± 237	194 ± 217	221 ± 253	211.2 ± 241.7	
Distance, km					0.219
Local	64 (26.0)	59 (24.0)	123 (50.0)	246 (100)	
< 150	38 (27.0)	18 (12.8)	85 (60.3)	141 (100)	
150 - 500	61 (24.0)	54 (21.3)	139 (54.7)	254 (100)	
> 500	23 (27.1)	15 (17.6)	47 (55.3)	85 (100)	
BMI, kg/m^2					
Mean ± SD	24.59 ± 4.71	24.7 ± 3.9	22.63 ± 4.11	23.55 ± 4.34	0.000
Rh					0.087
Negative	13 (20.6)	19 (30.2)	31 (49.2)	63 (100)	
Positive	173 (26.1)	124 (18.7)	366 (55.2)	663 (100)	
ABO					0.076
A	64 (26.1)	53 (21.6)	128 (52.2)	245 (100)	
AB	21 (32.8)	13 (20.3)	30 (46.9)	64 (100)	
B	36 (21.3)	23 (13.6)	110 (65.1)	169 (100)	
O	65 (26.2)	54 (21.8)	129 (52.0)	248 (100)	
Diabetes mellitus					0.074
Positive	55 (29.6)	42 (22.6)	89 (47.8)	186 (100)	
Negative	128 (23.6)	103 (19.0)	312 (57.5)	543 (100)	
Urologic disease					0.491
Positive	8 (29.6)	3 (11.1)	16 (59.3)	27 (100)	
Negative	174 (24.8)	142 (20.3)	385 (54.9)	701 (100)	
Congenital disease					0.908
Positive	7 (24.1)	5 (17.2)	17 (58.6)	29 (100)	
Negative	174 (25.0)	140 (20.1)	382 (54.9)	696 (100)	
Hypertension					0.870
Positive	93 (24.9)	78 (20.9)	203 (54.3)	374 (100)	
Negative	88 (25.0)	68 (19.3)	196 (55.7)	352 (100)	
Glomerulonephritis					0.979
Positive	7 (25.9)	5 (18.5)	15 (55.6)	27 (100)	

Negative	174 (24.9)	140 (20.0)	385 (55.1)	699 (100)	
Polycystic kidney disease					0.316
Positive	10 (16.9)	14 (23.7)	35 (59.3)	59 (100)	
Negative	171 (25.6)	131 (19.6)	365 (54.7)	667 (100)	
Infection					0.289
Positive	1 (25.0)	2 (50.0)	1 (25.0)	4 (100)	
Negative	178 (24.8)	142 (19.8)	397 (55.4)	717 (100)	
Renal stone					0.394
Positive	14 (25.0)	15 (26.8)	27 (48.2)	56 (100)	
Negative	164 (24.7)	130 (19.6)	370 (55.7)	664 (100)	
Hepatitis B					0.080
Positive	1 (9.1)	5 (45.5)	5 (45.5)	11 (100)	
Negative	182 (25.4)	139 (19.4)	396 (55.2)	717 (100)	
Hepatitis C					0.226
Positive	1 (100.0)	0 (0)	0 (0)	1 (100)	
Negative	182 (25.1)	143 (19.7)	401 (55.2)	726 (100)	
HIV					0.665
Positive	0 (0.0)	0 (0.0)	1 (100.0)	1 (100)	
Negative	183 (25.1)	144 (19.8)	401 (55.1)	728 (100)	
Cardiovascular disease					0.818
Positive	13 (27.1)	8 (16.7)	27 (56.3)	48 (100)	
Negative	166 (24.7)	136 (20.3)	369 (55.0)	671 (100)	
Year of transplantation					0.105
Before 2012	46 (19.1)	48 (19.9)	147 (61.0)	241 (100)	
2012	36 (29.5)	27 (22.1)	59 (48.4)	122 (100)	
2013	39 (23.1)	31 (18.3)	99 (58.6)	169 (100)	
2014	38 (28.8)	24 (18.2)	70 (53.0)	132 (100)	
2015	39 (31.0)	31 (24.6)	56 (44.4)	126 (100)	
2016	4 (17.4)	4 (17.4)	15 (65.2)	23 (100)	
Dialysis duration, y					0.104
< 1	40 (19.3)	53 (25.6)	114 (55.1)	207 (100)	
1 - 2	32 (17.3)	39 (21.1)	114 (61.6)	185 (100)	
> 2	32 (12.5)	55 (21.5)	169 (66.0)	256 (100)	
History of kidney transplantation					0.005
Positive	22 (42.3)	12 (23.0)	18 (34.6)	52 (100)	
Negative	177 (23.7)	158 (21.1)	411 (55.0)	746 (100)	
PPD					0.031
Positive	2 (7.6)	10 (38.4)	14 (53.8)	26 (100)	
Negative	197 (25.5)	160 (20.7)	415 (53.7)	772 (100)	

Abbreviations: BMI, body mass index; DGF, delay graft function; IGF, immediate graft function; SGF, slow graft function.
[a] Values are expressed as No. (%).