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ORIGINAL ARTICLE.

Living Donor Kidney Retransplantation: Risk Factors and Long Term Follow Up

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ABSTRACT

Background: Transplanting young and healthy individuals with ESRD maximizes survival outcome and saves money. Also Transplanting patients with co-morbidities is cost-effective and leads to significant survival outcome in comparison to the dialysis alternative. Although kidney re-transplantation is often accepted as the best choice for most patients subsequent to kidney allograft loss, there is surprisingly few data to support it. Our aim is to assess the outcome of living kidney re-transplantation and whether patients experiencing primary allograft loss should be offered the second renal allograft**.**

Methods: Comparative cross-section study included 267 recipients of kidney transplant who underwent kidney allo-transplantation from March, 1976 till December, 2015. These recipients were divided into two groups. Group1: All Patients who received 2nd kidney transplantation (90 patients). Group 2: Matched group of patients who received first kidney transplantation.

Results: Both groups were comparable in their demographic data but recipient consanguinity (p=0.000), donor age (p =0.004) and gender(p=0.000) were not comparable. As for maintenance therapy, while the total dose of steroid was comparable (p=0.28) , the percentage of use of different immune suppression protocols was significantly different in both groups(p=0.000). Regarding Post-transplant complications, no statistical difference has been found between both groups with regard to infections, hepatic impairment and malignancy (p< 0.05)while acute tubular injury incidence was higher in the study group (p=0.04).

Conclusions: our study is considered as a push for patients who lose their first graft to undergo second transplantation without fear of any further complication. Re-transplantation is safe and comparable with primary transplantation in all risk factors and outcomes..

Keywords: kidney , retransplant, risk , follow up

INTRODUCTION

Kidney transplantation is considered the best methodin management of ESRD, kidney transplant recipients have a much better quality of life and consume fewer resources in comparison to hemodialysis patients. [1] Although kidney re-transplantation is often accepted as the best choice for most patients subsequent to kidney allograft loss, there is surprisingly few data to support it. While outcomes after kidney transplantation have enhanced over the years, graft failure eventually occurs in many patients. Re-transplantation often provides the desirable outcomes in those patients, especially when compared with patients who are on maintenance hemodialysis. [2]

The graft failure risk after re-transplantation is significantly higher than the risk following primary transplants as the unadjusted 1-, 3- and 5-year graft survival rates following re-transplants (93%, 83% and 76%), were significantly less than the survival rate following primary transplant (95%, 89% and 81%, respectively) (p < 0.01, p < 0.0001, p = 0.01, respectively). [3]

The first graft survival has been considered a significant indicator of subsequent transplant outcome in several studies. [4]Both previous graft survival and the time to re-transplant have been significantly associated with regraft survival. [5]Furthermore, those who lost their primary allograft within 36 months post transplant were more susceptible to second allograft loss in comparison to those with a primary graft that lasted more than 36 months. [6]

Controversy exists about whether patients experiencing primary allograft loss should be offered the second renal allograft. This is an issue that has been heightened by exponential rise in patients waiting transplantation compared with the number of transplants performed each year. Therefore, our goal is to evaluate the outcome the re-transplantation and whether patients experiencing primary allograft loss should be offered the second renal allograft.

METHODS

Study design and population:267 renal transplant recipients were included in comparative cross-section study, those patients underwent kidney transplantation at Mansoura urology and nephrology Centre from March 1976 until December 2015.

These patients were divided into two main groups: I. All the patients who received second kidney transplantation (90 patients, study group).II. Matched group of patients who received first kidney transplantation (177 patients, control group).

Exclusion criteria: non-Egyptian renal transplant recipients and Lost follow up patients.

The transplant registry at the center was reviewed for both groups to assess the transplant outcome using univariate and multivariate analysis.

Records of the recipients were reviewed for: (a)pre-operative details such as Demographic data(the recipient age and sex, the donor age and sex, consanguinity), Causes of end stage renal disease (original kidney disease), Pretransplant dialysis, Pre- transplant medical disorders like hypertension, Immunologic data as regard HLA and DR mismatching.

(b)Operative details as ischemia time and time to diuresis.

(c)Post-operative details such as Induction immunosuppressive drugs, Maintenance immunosuppressive protocol, Frequency of acute and chronic rejection episodes, Post-transplantation medical disorders hypertension, diabetes mellitus, liver impairment, CMV disease, bacterial infection and malignancy which reflect over immune suppression, Mean serum creatinine over one, two and three years post-transplant, Condition of the patient at last follows up.

Immunosuppressive drugs: (a)Induction immunosuppression: Several different regimens of induction therapy have been given to patients:•Antithymocyte globulin (ATG) (IV infusion of 1.5 mg/kg/day given for 7 to 14 days).•Basiliximab :IV infusion of 20 mg over 20-30 minutes. •Alemtuzumab (Campath 1-H) (60 mg by slow IV infusion on day zero).

(b)Maintenance immunosuppression: All recipients received different regimens of immunosuppression which are: Conventional immunosuppression, Cyclosporine-based protocol, Campath protocol, Sirolimus-based protocol and Tacrolimus-based Protocol.

Graft function: During hospitalization, kidney function was monitored every day by:

creatinine clearance, serum creatinine, urine analysis, Graft grey-scale ultrasonography and graft Doppler to evaluate graft perfusion and resistive index.

Written informed consent was obtained from all participants, the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The study was done according to The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis:

The record, tabulation and analysis of the collected data has been done using SPSS for windows (SPSS inc. Chicago). The continuous data between the two groups were compared using T test. Chi square test was used to compare categorical data. The Kaplan- Meier technique has been used to compute the graft and patient survival. P-value < 0.05 was considered statistically significant.

RESULTS:

267 allograft recipients have been included in our study. Patients have been divided as study group (second transplant) (90patients) and a control group (one transplant) (177 patients). Regarding demographical data, both groups were comparable in their demographical data such as recipient age (p=0.502),recipient gender (p=0.805) and recipient age (p=0.9) while recipient consanguinity(p=0.000), donor age(p=0.004)and donor gender (p=0.000) were significantly different between the two groups as illustrated in Table (1). Moreover we did not find any significant difference between both groups with regard to HLA class II (DR) matching (p=0.45) and blood group (p=0.151) ,while there was a statistically significant difference regarding HLA class I matching between both groups (p=0.009)

as shown in Table (2).As for immunosuppression therapy, the induction immunosuppression was significantly different between the two groups (p=0.001), the percentage of ATG use in study group(45.5%) was higher than control group (6%) and Basiliximab was mainly used in control group(89%)compared to (45.4%) in the study group as shown in Table (3).There were different immunosuppression protocols for maintenance therapy as discussed in Table (3).While the total dose of steroid was comparable between both groups (p=0.28),the percentage of use of different immunosuppression protocols was significantly different in both groups(p=0.000).Regarding Post-transplant complications, no statistical difference has been found between both groups with regard to hypertension, DM, bacterial infection, viral infection, hepatic impairment and malignancy (p > 0.05) while acute tubular injury incidence was higher in the study group (p=0.04) as illustrated in Table(4)

Table 1: Comparison of Demographic data in the two groups

Pretransplant characteristics	GroupI(n=90)	GrouII (n=177)	P-value
Recipient age(Mean±SD) Years	34.31±9.868	33.5±9.082	0.502 NS*
Recipient gender(Male/Female, frequency)	66/24	133/44	0.805 NS**
Donorage (Mean±SD)years	32.5±7.906	36.11±10.342	0.004 S*
Donor gender (Male/Female, frequency)	60/30	73/104	0.000 S*
Recipient age by group(years)			
<20	6(6.7%)	14(7.9%)	0.9 NS**
20-30	31(34%)	58(32.8%)	
30-40	29(32.2%)	63(35.6%)	
>40	24(26.7%)	42(23.7%)	
Consanguinity:			
Related	38(42.2%)	150(84.7%)	0.000 S*
Unrelated	52(65.8%)	27(34.2%)	

(*)S=significance,(**)NS=nonsignificance

Table 2: Comparison of HLA class I ,HLA class II and blood group in the two groups

	GroupI(n=90)	GroupII(n=177)	P-value
A)HLA classI matching			
Zero	5(5.5%)	24(13.5%)	0.009 S**
mismatchOne	6(6.6%)	27(15.2%)	
mismatchTwo	31(34.4%)	64(36.1%)	
mismatchThreem	31(34.4%)	33(18.6%)	
ismatchFour	6(5.6%)	13(7.3)	
mismatch	13(14.4%)	16(9%)	
Inapplicable			

B)HLAclassII(DR)matching Zero mismatch One mismatchTwomismatch	7(7.9%) 81(91%) 2(2.2%)	152(89%) 22(11%) 3(1.6%)	0.45 NS**
Blood group same Different	65(72.2%) 25(27.8%)	143(80.8%) 34(19.2%)	0.151 NS**

HLA;Human leukocyte antigen

Table 3: Immunosupression protocol:induction and maintenance therapy

	GROUPI(n=90)	**Group II(n=177)**	**P-value**
Induction therapy			
Basiliximab	**49(45.4)**	**158(89%)**	.001 **S***
ATG	**41(45.5%)**	**11(6%)**	
Almetuzumab	**0**	**8(4.5%)**	
Maintenance therapy			
Total dose of steroid in grams in the first three months (gram,Mean ± SD)	**5.07±2.34**	**4.9±2.7**	0.28 **NS****
Azathioprine-based	**1(1.1%)**	**22(12.4%)**	0.000 **S***
Tacrolimus-based	**37(41.1%)**	**34(19%)**	
Cyclosporine-based	**45(50%)**	**103(58%)**	
Sirolimus based	**7(7.8%)**	**18(10%)**	

ATG:anti-thymocyteglobulinOKT3:orthaclone

Table 4: Comparison of post transplant complications in both groups**.**

Posttransplantcomplications	GroupI (n=90)	GroupII (n=177)	P-value
Hypertension			
Yes No	47(52.2%) 43(41%)	101(57.1%) 76(42.9%)	0.267 NS**
Diabetes mellitus			
Yes No	18(20%) 72(80%)	42(23.7%) 135(76.3%)	0.49 NS**
Hepatic impairment			
Yes No	7(7.8%) 83(92.2%)	12(6.8%) 165(93.2%)	0.962 NS**
Bacterial Infection			
Yes No	18(20%) 72(80%	24(13.6%) 153(86.4%)	0.118 NS*
Viral infection			
Yes No	9(10%) 81(90%)	15(8.5%) 162(91.5%)	0.41 NS**
Malignancy			
Yes No	4(4.4%) 86(95.6%)	14(7.9%) 163(92.1)	0.43 NS**
Graft nephrectomy			
Yes No	3(3.3%) 87(96.7%)	6(3.4%) 171(96.6)	1 NS**
ATN			
Yes No	6(6.7%) 84(93.3%)	3(1.7%) 174(98.3%)	.04 S*

DISCUSSION

Kidney transplantation is considered the treatment of choice for patients suffering ESRD, but because the long-term survival of renal allograft is limited, most of transplant recipients will experience graft loss and will be considered for a re-transplantation. [7]Several issues may influence the outcomes of re-transplantation, and the most significant one is the cause of the prior transplant failure. [8]Despite the fact that outcomes following the primary transplant may be more likely to recur after a retransplant, since the associations between primary transplant outcomes and overall retransplant graft survival are not significant, this knowledge is relevant to clinical practice regarding treatment strategy for recipients of failed primary transplants. [9]Our retrospective analysis of 267 Egyptian renal transplant recipients addressed the immunological and medical outcomes of second kidney transplantation and its effect on both graft and patient. Patients in our study have been divided into two groups; Group I (90 patients that received their second kidney transplantation), Group II (177 matched patients who received first kidney transplantation). We only consider Living-donor renal transplantation in our transplantation program for either primary or retransplants.

In our study, we found that recipient sex and age does not seem to affect graft survival which cope

with registry data from the United Network of Organ Sharing which reported that the survival rates are similar for males and females. [10]

As regard to Oien et al., 2007 they supported the continuous use of elderly male and female living donors that fulfil clinical criteria and who are strongly motivated to donate. [11] Moreover, the age of the donor is likely to be a much more significant determinant of the probability of the graft loss than the gender of the donor which cope with the results in our study which revealed that donor age has a significant value which may affect the graft survival outcome but there was no significant value as regard to donor gender although different studied reported that female recipients of male kidneys have an inferior graft survival. The survival outcome for recipients of graft from living unrelated donor appears to be similar to that from zero haplo type-matched living related donors and is similar to that achieved with cadaveric transplants. [12] We observed that the relationship between the recipient and his donor appeared to have a significant value for repeat transplantation. The percentage of unrelated donor in second transplants (65.8%) was higher than those in primary transplant recipients (34.2%) which are accepted in our policy of second transplantation after failure of the first graft from a related one.

In our study, no significant difference has been found between the two groups with regard to the original kidney disease which is important factor that may affect the survival as discussed in Mashaly et al., 2016 they documented that the original kidney disease has statistical significance regarding both the allograft survival and patient survival. [13]

In accordance with Florit et al., 2015 Pre-emptive kidney re-transplantation is considered a possible choice that need to be evaluated in those with renal graft failure which mightlead to decrease the morbidity related to reinitiating the hemodialysis. [6]Due to the profound graft shortage this strategy is limited to those with a living donor.

Pre-emptive second transplantation didn't take place in our study, unfortunately all patients in our study group started dialysis before re-transplantation. Successful result of the transplantation depends on many important factors; one of which is the donor – recipient immunological compatibility. [14]In our study the immunological workup before transplantation as regard matching for HLA-DR antigen was comparable in the two groups with statistically difference in HLA class I (p= 0.009).In our study, the use of ATG had a greater percentage in the second transplant group (45.5%) as they might be considered in case of high risk of rejection and early graft dysfunction which is in line with Karen L. Hardinger et al., 2012 which reported that lots of centers are reluctant to use potent induction therapy due to the risk of infections or malignancy and shortage of long-term data that show a graft survival benefit. [15]Schold et al., 2015 reported that the outcomes related to induction treatment between recipients of kidney retransplant in the USA are variable, which include more graft loss rates among those who were treated with Almetuzumab but similar survival outcomes between all regimens. [16] The One-year survival of kidney allograft in many centers is currently around 80% to 90%; and the survival rate of other organs are now near this proportion. [17]The maintenance immunosuppression drugs in both groups had statistical significance (p= 0.000) but there was no statistical significance between both groups with regard to total steroid dose in the first three month, triple immunosuppression protocols were used in both groups, the majority of cases used CNI as a mainstay drug whenever tacrolimus based protocol has the higher percentage in second transplant group (41.1%) and cyclosporine based protocol has the higher percentage in control group (58 %).

The incidence of rejection episodes was comparable in two groups that may influenced by previous variable risk factors that have no significant difference between both groups as discussed in Moes DJ et al., 2016. [18] Despite the advances in immunosuppressive drugs, which have significantly led to improvement in short-term graft outcomes and acute rejection in recipients of renal transplant, yet long-term graft survivalhas not significantly increased. Moreover, those recipients have a significant risk of malignancy; CVD, infection, and diabetes, which all increase the morbidity and premature mortality. [19]

Hypertension is a common problem which is frequently observed following renal transplantation due to many causes. In our study, pre-transplant hypertension was diagnosed in 58.9%% in retransplant group and in 63.3%% in first transplant group (p= 0.507). And the prevalence of post-transplant hypertension was also comparable between the two groups post transplantation (p= 0.267) which agree with Soypacacia et al., 2013. [20] Moreover, Post transplantation hypertension increases the incidence of both cardiovascular diseases and allograft failure. Despite the fact that a low sodium diet is strongly advised, the relationship between it and post transplantation hypertension

has not been well studied in transplant patients. We observed post-transplantation diabetes mellitus (PTDM) in 20% in second transplants and in 23.7% in first transplants(p= 0.49) which didn't cope with the expectation regarding the larger cumulative dose of different immunosuppressive drugs including steroids in patients who received their second graft .Improvement of those drugs and close monitoring of their levels with regular follow up of patients and rapidly diagnose early glucose intolerance or any occult hyperglycemia may improve the outcome in both groups so, there was no significant difference regarding occurrence of post-transplant diabetes .The influence of post-transplant diabetes in either patient or graft survival was discussed by Gaynor et al.,2015 and they demonstrated that there was a less than-expected post-NODAT risk for graft loss and death in the current climate of tighter glucose monitoring post transplant. [21]

No significant difference has been found in our study between the two groups as regard of the incidence of infection either bacterial (p= 0.11) or viral (p= 41) infection, in general infection is an important and highly prevalent complication in our transplant patient who use potent immunosuppressive drugs, the higher use of ATG as induction therapy in second transplant group might increase that risk especially CMV infection which is still a serious problem with thymoglobulin induction in spite of six months of valganciclovir as discussed before. [22]

Cancer is considered a common complication following renal transplant and the second cause of mortality in those recipients. [23]It has been reported that the overall incidence of cancer following renal transplant is three to five times more than the general population. [24]

According to Helmy et al., 2016 there is a five times increased risk of many types of cancer including Kaposi sarcoma, liver , skin, GIT, and lung cancer following transplantation. [25] Our study showed that the incidence of malignant tumors were comparable between the two groups (p= 0.43).

In conclusion, our study is considered as a push for patients who lose their first graft to undergo second transplantation without fear of any further complication. By following a large number of retransplants with a matched group of primary transplants over variable periods of time lasting for 30 years we concluded that re-transplantation is safe and comparable with primary transplantation in all risk factors and outcomes. Nowadays with improvements and advances in immunosuppressive drugs and good control of their levels, graft survival rates are improved also with primary and re-transplantation. Good selection of the donor with the lowest immunological risk factors with good preparation before transplantation, the usage of potent induction therapy and the strong maintenance immunosuppressive drugs are important factors for graft and patient survival.

REFERENCES

1-Yoo, S., Kwon, O., & Kang, C. Preemptive Living-Donor Renal Transplantation: Outcome and Clinical Advantages. TransplantProc.2009, 41(1), 117-120.

2-Koch, M.. Considerations in Retransplantation of the Failed Renal Allograft Recipient. Adv Chronic Kidney Dis.2006,13(1), 18-28.

3-Magee, J., Barr, M., Basadonna, G., Johnson, M., Mahadevan, S., & McBride, M. et al. . Repeat Organ Transplantation in the United States, 1996?2005. Am J Transplant.2007 ,7(s1), 1424-1433. **4-Arnol, M., Prather, J., Mittalhenkle, A., Barry, J., & Norman, D..** Long-Term Kidney Regraft Survival From Deceased Donors: Risk Factors and Outcomes in a Single Centre. Transplantation,2008, 86(8), 1084-1089.

5-Arndorfer, J., Meier-Kriesche, H., Ojo, A., Gruber, S., Cibrik, D., & Lake, K. et al. Time to first graft loss as a risk factor for second renal allograft loss. TransplantProc.2001, 33(1-2), 1188-1189. **6-Florit, E., Bennis, S., Rodriguez, E., Revuelta, I., De Sousa, E., & Esforzado, N. et al.** Pre-Emptive Retransplantation in Patients With Chronic Kidney Graft Failure. Transplant Proc.2015, 47(8), 2351-2353.

7-Kousoulas, L., Vondran, F., Syryca, P., Klempnauer, J., Schrem, H., & Lehner, F. Risk-Adjusted Analysis of Relevant Outcome Drivers for Patients after More Than Two Kidney Transplants. J Transplant, 2015, 1-9.

8-Graves, R., & Fine, R.. Kidney retransplantation in children following rejection and recurrent disease. Pediatr Nephrol.2016,31(12), 2235-2247.

9-Heaphy, E., Poggio, E., Flechner, S., Goldfarb, D., Askar, M., & Fatica, R. et al.. Risk Factors for Retransplant Kidney Recipients: Relisting and Outcomes From Patients' Primary Transplant. Am J Transplant.2014, 14(6), 1356-1367.

10-UNOS organ procurement and transplantation network data. United Network for Organ Sharing Web site. Sept 17, 2004.

11-Øien, C., Reisæter, A., Leivestad, T., Dekker, F., Line, P., & Os, I. Living Donor Kidney Transplantation: The Effects of Donor

Age and Gender on Short- and Long-Term Outcomes. Transplantation, 2007,83(5), 600-606.

12-Sesso, R. Kidney Transplantation from Living Unrelated Donors. Ann Intern Med.1992, 117(12), 983.

13-Mohamed E. Mashaly, Mabrouk I. Ismail, Esam E. Lotfy, et al. "Frequency of the Original Kidney Disease and Its Effect on the Outcome of Kidney Transplant in the Urology-Nephrology Center Mansoura University". Exp Clin Transplant. 2016 Apr;14(2):157-65.

14-Koukoulaki, M., Kitsiou, V., Balaska, A., Pistolas, D., Loukopoulos, I., & Drakopoulos, V. et al. Immunologic Prognostic Factors of Renal Allograft Survival. Transplant Proc.2014,46(9), 3175-3178.

15-Hardinger, K., Brennan, D., & Klein, C.. Selection of induction therapy in kidney transplantation. Transpl Int.2012, 26(7), 662-672.

16 -Meier-Kriesche, H., & Schold, J. The Impact of Pretransplant Dialysis on Outcomes in Renal Transplantation. Semin Dial.2005, 18(6), 499-504

17-Denton, M., Magee, C., & Sayegh, M. . Immunosuppressive strategies in transplantation. Lancet,1999, 353(9158), 1083-1091.

18-Moes, D., Press, R., Ackaert, O., Ploeger, B., Bemelman, F., & Diack, C. et al. Exploring genetic and non-genetic risk factors for delayed graft function, acute and subclinical rejection in renal transplant recipients. Br J Clin Pharmacol.2016,82(1), 227-237.

19-Tong, A., Budde, K., Gill, J., Josephson, M., Marson, L., & Pruett, T. et al. Standardized Outcomes in Nephrology-Transplantation: A Global Initiative to Develop a Core Outcome Set for Trials in Kidney Transplantation. Transplant Direct.2016, 2(6), e79.

20-Soypacaci, Z., Sengul, S., Yıldız, E., Keven, K., Kutlay, S., Erturk, S., & Erbay, B.. Effect of Daily Sodium Intake on Post-transplant Hypertension in Kidney Allograft Recipients. Transplant Proc2013,. 45(3), 940-943.

21-Gaynor, J., Ciancio, G., Guerra, G., Sageshima, J., Hanson, L., & Roth, D. et al.. Single-centre study of 628 adult, primary kidney transplant recipients showing no unfavourable effect of new-onset diabetes after transplant. Diabetologia, 2014,58(2), 334-345

22-Puttarajappa, C., Bhattarai, M., Mour, G., Shen, C., Sood, P., & Mehta, R. et al. Cytomegalovirus infection in high-risk kidney transplant recipients receiving thymoglobulin induction-a single-center experience. Clin Transplant.2016, 30(9), 1159-1164.

23-Navarro, M., López-Andréu, M., Rodríguez-Benot, A., Agüera, M., Del Castillo, D., & Aljama, P. Cancer Incidence and Survival in Kidney Transplant Patients. Transplant Proc. 2008, 40(9), 2936-2940.

24-Birkeland, S., L⊘kkegaard, H., & Storm, H. Cancer risk in patients on dialysis and after renal transplantation. Lancet,2000, 355(9218), 1886-1887.

25-Helmy, S., Marschalek, J., Bader, Y., Koch, M., Schmidt, A., & Kanzler, M. et al.. Risk Factors for De Novo Malignancies in Women After Kidney Transplantation: A Multicenter Transversal Study. Int J Gynecol Cancer.2016,26(5), 967-970.

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