Original Article

Causes of Graft Dysfunction in Live Related Kidney Transplantation in a Tertiary Care Hospital

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ABSTRACT

Introduction: *Renal transplantation remains the treatment of choice for end-stage renal disease (ESRD). Graft dysfunction or adverse events following renal transplantation are associated not only with short & long term graft outcome, but also with patient survival. Living kidney donation is a scheduled event that offers the advantage of optimal preparation for the recipient and donor. Restoration & preservation of renal function post transplant depends on many factors. Attempts should therefore been made to improve early graft function by a variety of mechanical, pharmacological and organ allocation strategies.*

Objectives: *To identify the causes of graft dysfunction in renal allograft recipients.*

Method: *In this prospective study, a total of 40 renal allograft recipients as well as 40 donors were evaluated. ESRD patients and kidney donors preoperative details and clinical parameters were recorded in structured questionnaire. Peroperative variables like induction with antibody, cold ischemia time, warm ischemia time, peroperative hypotension, peroperative blood transfusion, peroperative urine production were recorded. Early postoperative clinical variables like BP, hourly urine production, temperature were monitored and biochemical Hb%, Tc, Dc, ESR, blood urea, serum creatinine, s. electrolytes, cyclosporin level (C_2 level), urine RME & CS and imaging USG of transplanted kidney and duplex study of renal vessels were done. On the basis of creatinine reduction ratio(CRR) on post transplant day 7, renal allograft recipients were divided into IGF and RGF/graft dysfunction group respectively and evaluation and causes of graft dysfunction were recorded. Data were processed and analyzed using computer software SPSS (Statistical package for social science) version 12.*

Results: *The mean age of donors was 39.15±10.09 years with a male female ratio 1:1.7. The mean age of renal allograft recipients was 32.30±8.85 years with a male to female ratio of 3.5:1. Among 40 patients, 52.5% recipients had IGF and 47.5% had RGF. At day 7 posttransplantation period mean serum creatinine in IGF group was 130.10±14.45 ìmol/L and in RGF group was 237.32±123.85 ìmol/L which was statistically strongly significant (p value <0.0001). Regarding causes of graft dysfunction at day 7 post transplant period, cold ischemia time (p value 0.043) and postoperative urine production within 6 hours (p value 0.0001) were found statistically significant.*

Conclusion: *This study showed that 52.5% renal allograft recipient had IGF and 47.5 % renal allograft recipient had graft dysfunction(RGF). Significant causes of graft dysfunction were long cold ischemia time in minute and peroperative urine production in ml within 6 hours after anastomosis of vessels.*

Keywords: *Kidney transplantation, Immediate graft function (IGF), Reduced graft function (RGF), Graft dysfunction.*

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INTRODUCTION:

Renal transplantation remains the treatment of choice for end-stage renal disease (ESRD) in regards to patient survival[1]. Marked improvements in early graft survival, short-term and long-term graft function have translated into kidney transplantation being a more cost-effective alternative to dialysis. Post-transplantation graft function usually divided into immediate graft function (IGF) and poor early graft function or delayed graft function (DGF) or reduced function group(RGF). **Olwyn Johnston** *et al.* 2006[2] in their study divide graft function in reduced graft function (with or without dialysis) and immediate graft function. 7 days' creatinine reduction ratio (CRR) marked as cut point of difference between immediate graft function (IGF) & reduced graft function (RGF) group. Recipients with a CRR between time 0 of transplantation and day 7 post-transplantation of e"70% had IGF and CRR <70% with or without dialysis had RGF. RGF may subdivided into DGF where CRR <70% with dialysis and SGF where CRR <70% without dialysis.

Restoration & Preservation of renal function post-transplant depends on many factors. Long- term success of renal transplantation depends upon the quality of the donor organ, avoidance of peritransplant and early posttransplant damage and optimal maintenance of graft function after the first 6-12 months[3]. Living donation is a scheduled event that offers the advantage of optimal preparation for the recipient and donor. This situation allows for control of logistics that minimize the organ preservation time. Risk factors for DGF in the recipient include male gender, black race, longer dialysis duration, high panel-reactive antibody (PRA) titer, CMV status, number of grafts received and greater degree of HLA mismatching. Donor related risk factors include use of cadaveric donors, older donor age and longer cold ischemia time[4]. Most of these variables affect the graft through ischemia-reperfusion injury and immunologic mechanisms. High dosage of calcineurin inhibitors (CNIs) could also prolong or worsen DGF[5]. Humar A *et al*.2002[6] in their study showed that initial function of the graft significantly influenced the subsequent risk of acute rejection (at 12 months' post-transplant, the incidence of AR was 28% for those with IGF, 38% for those with SGF, and 44% for those with DGF) and graft survival (the 5-yr death-censored graft survival rate was 89% for recipients with IGF, 72% for those with SGF, and 67% for those with DGF). Attempts should therefore been made to improve early graft function by a variety of mechanical, pharmacological and organ allocation strategies[7]. If suboptimal early graft function could be accurately predicted, the success of these strategies may be improved. Hence, the present study was proposed to identify the causes of graft dysfunction in renal allograft recipients.

METHODS:

This prospective observational study was done in department of Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU) over a period of 36 months from January 2010 to December 2012. A total of 40 renal allograft recipients as well as 40 kidney donors were included in this study. ESRD patients and kidney donors preoperative details and clinical parameters were recorded in structured questionnaire. All patients (except preemptive transplantation) received hemodialysis on the day before transplantation. Immunosuppressive drugs Cyclosporin and MMF were started 2 days before transplantation. Inj. Basiliximab 20 mg peroperatively and Day 4 posttransplantation – if indicated. Peroperative variables like induction with antibody, cold ischemia time, warm ischemia time, peroperative hypotension, peroperative blood transfusion, peroperative urine production were recorded.

All vital signs including BP, hourly urine production, temperature were monitored hourly and intake-output chart was maintained according to protocol in post-operative period on the day of operation in KT-ICU. During 1-7 days post-operative period, all vital signs were monitored at regular interval, intake-output chart and fluid balance were maintained according, I.V Methyl prednisolone – 1st & 2nd POD, oral Cyclosporin , oral MMF and oral prednisolone were used as immunosuppressive agents. Any symptoms of fever, burning sensation during micturation, cough etc. were noted. Foleys cather removed on 3rd POD. Laboratory investigations were daily Urine routine and microscopic examination, Hb%, TC, DC, ESR, B. Urea, S. Creatinine, S. Elecrolytes. Urine C/S- 3rd POD, Duplex study of the anastomotic vessels on 5th day, C_2 level (Blood level of cyclosporine 2 hours after ingestion) on 7th day. Other investigations were done according to need like blood C/S, USG of the transplanted kidney etc. On the basis of creatinine reduction ratio(CRR) on post transplant day 7, renal allograft recipients were divided into IGF and RGF group respectively and evaluation and causes of graft dysfunction were recorded.

RESULT:

Table I: *Preoperative characteristics of donors (n=40)*

Parameters	Mean±SD	Frequency	Percentage
Age (years)	39.15±10.09		
Sex			
Male		15	37.5
Female		25	62.5
Creatinine clearance rate (ml/min)	84.03±17.61		
Anti CMV (IgM)			
Positive		0	0.0
Negative		40	100.0
Anti CMV (IgG)			
Positive		35	87.5
Negative		5	12.5

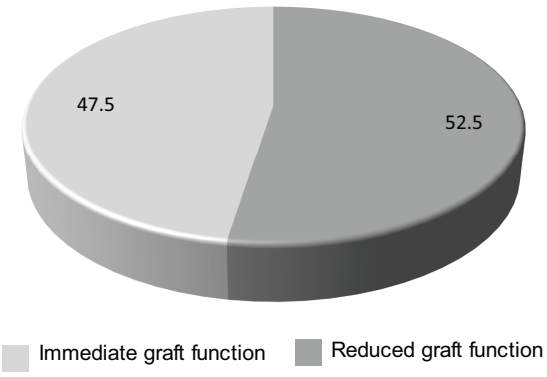

Fig.1 *Recipients graft status at 7th post transplant day*

Table II: *Preoperative characteristics of recipients (n=40)*

Parameters	Mean±SD	Frequency	Percentage
Age (years)	32.30±8.85		
Sex			
Male		31	77.5
Female		9	22.5
Pretransplant serum creatinine (μmol/L)	523.23±109.77		
HLA typing (class I)			
4 mismatch		6	15.0
2 mismatch		33	82.5
0 mismatch		1	2.5
Anti CMV (IgM)			
Positive		2	5.0
Negative		38	95.0
Anti CMV (IgG)			
Positive		36	90.0
Negative		4	10.0

Fig.1 shows recipients graft status at 7th posttransplant day. 52.5% recipients had immediate graft function and 47.5% had graft dysfunction or reduced graft function.

Table III: *Comparison of postoperative serum creatinine level between reduced and immediate graft function groups*

Serum creatinine (μmol/L)	Reduced graft function (n=19) (Mean±SD)	Immediate graft function (n=21) (Mean±SD)	p value[a]
At day 7	237.32±123.85	130.10±14.45	0.0001***

[a]Unpaired Student's 't' test
ns = Not significant
* = Significant at P<0.05
** = Significant at P<0.01
*** = Significant at P<0.001

Table IV: *Comparison of recipient peroperative risk factors between reduced and immediate graft function groups*

Risk factors	Reduced graft function (n=19)	Immediate graft function (n=21)	p value
[a]Induction with antibody			0.301[ns]
Yes (No./%)	6 (31.6)	10 (47.6)	
No (No./%)	13 (68.4)	11 (52.4)	
[b]Cold ischaemic time(min)			
(Mean±SD)	108.11±123.45	51.57±11.68	0.043[*]
[b]Warm ischaemic time(sec)			
(Mean±SD)	13.68±3.13	13.76±2.41	0.930[ns]
[c]Peroperative hypotension			0.0001[***]
Yes (No./%)	10 (52.6)	0	
No (No./%)	9 (47.4)	21 (100.0)	
[c]Peroperative blood transfusion		0.005[**]	
Yes (No./%)	11 (57.9)	3 (14.3)	
No	8 (42.1)	18 (85.7)	
[b]Urine production(ml)			
(Mean±SD)	83.84±112.62	354.52±215.84	0.0001[***]

[a]Chi square test ns = Not significant [b]Unpaired Student's 't' test
* = Significant at P<0.05 [c]Fisher's exact test ** = Significant at P<0.01
*** = Significant at P<0.001

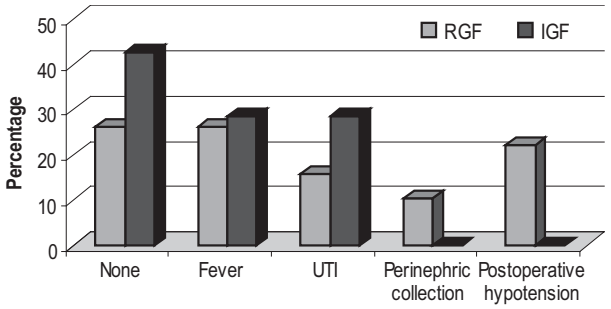

Fig. 2: *Adverse events at day 7*

Figure 2 shows adverse events at day 7. In RGF group, 21.1% patients suffered from postoperative hypotension. Fever was found in one quarter (26.3%), UTI in 15.8% and perinephric collection in 10.5% of patients. 26.3% patients of RGF group had no adverse events. In IGF group, about half of the patients had no adverse events whereas fever and UTI was observed equally in 28.6% patients.

Table V *Analysis of risk factors for reduced graft function (n=19) vs immediate (n=21) graft function groups*

Variables	Reduced graft function (n=19) No.(%)	Immediate graft function (n=21) No.(%)	RR (95% CI)	p value
[a]Donor age	41.05±9.8	37.43±10.26	36.02 42.46	0.262[ns]
[a]Recipient age	31.16±8.13	33.33±9.54	29.39 35.10	0.445[ns]
[a]Donor creatinine clearance rate	83.47±17.29	84.53±18.31	78.29 89.72	0.851[ns]
[a]Recipient pretreatment s. creatinine	513.47±115.72	532.05±106.18	487.25 558.27	0.600[ns]
[a]Cold ischaemic time	108.11±123.45	51.57±11.68	52.47 107.20	0.043[*]
[a]Warm ischaemic time	13.68±3.13	13.76±2.41	12.84 14.61	0.930[ns]
[a]Urine production(ml)	83.84±112.62	354.52±215.84	163.19 275.18	0.0001[***]
[b]Well matched kidney	18(94.6)	16(76.2)	0.333 (0.025 4.401)	0.404[ns]
[b]Induction with antibody	6 (31.6)	10(47.6)	0.625 (0.089 4.400)	0.637[ns]
[b]Peroperative hypotension	10(52.6)	0	0.0001 (0.000 0.032)	0.759[ns]
[b]Peroperative blood transfusion	11(57.9)	3(14.3)	0.563 (0.061 5.217)	0.613[ns]

[a]Multivariate analysis ns = Not significant
[b]Logistic regression * = Significant at P<0.05
*** = Significant at P<0.001

DISCUSSION:

Renal transplantation improves the patient's quality of life to a greater extent than hemodialysis and peritoneal dialysis[8]. Reduced Graft Function (RGF) is a well-known complication that can affect the kidney allograft in the immediate post-transplant period. Excellent organ quality and ideal transplant conditions contribute to immediate graft function (IGF) in a vast majority of living donor kidney transplantations (LDKT). However, poor early graft function still occurs after LDKT, although less frequently than after deceased donor kidney transplantation[9]. Poor EGF following LDKT has a large impact on long-term graft survival.[10]

For the purpose of the study, immediate graft function (IGF) was defined as return of normal renal function within 7 days after transplantation or creatinine reduction ratio (CRR)e" 70% on day 7 after transplantation, delayed graft function (DGF) as the requirement for dialysis within the first week after renal transplantation and slow graft function (SGF) as CRR< 70% on day 7 after transplantation without dialysis. Graft dysfunction or reduced graft function was defined as occurrence of DGF or SGF. In this study, at 7 days posttransplantation period mean serum creatinine in IGF group was 130.10±14.45 ìmol/L and in RGF group was 237.32±123.85 ìmol/L which was statistically strongly significant (p value <0.0001). Among 40 patients, 52.5% recipients had immediate graft function and 47.5% had reduced graft function.

Comparing the demographic characteristics between the study groups, age of both donor and recipient were found not significant. This is because most of the donors and recipients in our study were young adult. Mean age of donor was <40 years (39.15±10.09 years, range 22-60 yrs) and recipient was <33 years (32.30±8.85 years, range 15-50 yrs). It has been showed in different studies that older donor age is a risk factor for decrease graft survival. Senel FM *et al.*1998[11] and Cecka JM 1998[12] in their studies identified donor age >60 years as a risk factor. Fuggle SV *et al*.2010[13] described the association between donor age older than 59 years with poorer outcome after live donor kidney transplantation. But H.S. Park *et al*. 2012[14] showed there was no significant effect of donor age and recipient age on early graft function. In their study donor mean age was <42 years and recipient mean age<37 years which were almost similar to our study.

Regarding sex of donor and recipient, among the donors, 37.5% were male and 62.5% were female and the ratio of male and female was 1:1.7. In case of recipient, 77.5% of them were male and 22.5% were female. The ratio of male and female was about 3.5:1. Senel FM *et al.*1998 in their study[11], identified recipient sex as a risk factor for DGF. But some large studies showed that sex of both donor and recipient had no effect on graft function[14-15]. In our study, we did not find any significant effect of sex on graft function (p value in case of donor was 0.597 and in recipient was 0.431) which supports the recent studies.

In our study, regarding HLA matching between donor and recipient, 0 mismatch was found in 2.5% cases, 2 mismatch in 82.5% and 4 mismatch found in 15% cases. Univariate analysis between RGF and IGF groups showed no significant difference (p value 0.600). Logistic regression showed HLA mismatching was not a significant cause of RGF (p value 0.404). HLA matching was thought to be very important for living donors, given that two-haplotype–matched sibling donors have the best outcome. However, in the mid-1990s, results from a large registry analysis found that transplants from two-haplotype–mismatched siblings or spouses had outcomes similar to one haplotype– mismatched sibling or parental donor transplants. H.S. Park *et al*. 2012[14] showed there was no significant effect of HLA matching on early graft function.

Duration of cold ischemia time is a significant risk factor in the etiology of ATN and an increased ischemia time in cadaver transplantation is the cause of high incidence of ATN[16]. The anastamosis time has also been strongly correlated with de-layed graft function and was identified as the strongest independent predictor of delayed graft function in some studies.[17] In our study, cold ischemia time was defined as starting of cold solution perfusion after organ procurement and ends after establishment of recirculation after anastomosis of vessels in recipient which by definition includes the anastomosis time. Mean cold ischemia time in RGF group was 108.11±123.45 min and in IGF group was 51.57±11.68 which were statistically significant in univariate analysis (p value 0.043). Multivariate analysis showed cold ischemia time was an important risk factor for RGF (p value 0.043). In a study by Olwyn Johnston *et al*.2006[2] revealed that longer CIT are important risk factors for reduced graft function. Other

centres have also shown that longer CIT has an inûuence on graft survival.[18-20] Our result supported all of these study result.

Intraoperative hypotension and prolonged operative time are independent risk factors for SGF in kidney transplant patients.[21] For good graft function recovery, proper blood pressure (10-20mmHg (1mmHg= 0.133kPa) above the basic blood pressure) that ensures oxygenated blood is necessary. G. Bacchi, *et al*. 2010[22] also reported that reduced intraoperative perfusion as measured using CVP monitoring might increase DGF risk. In our study, peroperative hypotension and peroperative blood transfusion was significant in univariate analysis (p value 0.0001 and 0.005 respectively). But in logistic regression analysis both of these factors were not significant (p value 0.759 and 0.613 respectively). This was because preoperative hypotension was reversed immediately with blood transfusion and other measures.

KDIGO clinical practice guideline for the care of kidney transplant recipients stated that increased urine volume represents the ûrst sign of progressive recovery of kidney function, ahead of a decrease in serum creatinine or blood urea nitrogen. High urine volume during the first posttransplant days is a useful parameter to predict graft outcome.[23,24] Matteucci *et al*. 1998[23] also demonstrated a direct relation between serum creatinine and diuresis volume and urine creatinine after kidney transplantation. According to urine output criteria and relation with s. creatinine DGF was defined as rise in serum Cr at 6–8 h post-operatively or <300 ml of urine despite adequate volume and diuretics.[25] Or Urine output <1 L in 24 h and <25% fall in serum creatinine from baseline in first 24 h post-transplant.[26] In our study, mean urine output within 6 hours after anastomosis of renal vessels was 83.84±112.62 ml in RGF group and 354.52±215.84 ml in IGF group which was statistically highly significant (p value 0.0001). Lai Q *et al*.2010 in their study also showed UO had significant role in graft function. In that study, urine output was <500 ml / 24 hrs in 40% of patients of DGF group and only in 3% patients of IGF group.

CONCLUSION:

Graft dysfunction or adverse events following renal transplantation are associated not only with short & long term graft outcome, but also with patient survival. This study showed that 52.5% renal allograft recipient had IGF and 47.5 % renal allograft recipient had graft dysfunction(SGF). Significant causes of graft dysfunction were long cold ischemia time in minute and peroperative urine production in ml within 6 hours after anastomosis of vessels.

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