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Long-term outcome of kidney transplantation from deceased donors with early graft dysfunction: a single-center analysis

KEYWORDS: Kidney transplantation, Early graft dysfunction, Graft survival

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ABSTRACT *Objective The purpose of this stusy was to investigate the correlation factors for early graft dysfunction after kidney transplantation, and the effects on long-term graft survival.*

Methods Two hundred and fifty-one recipients of first cadaveric renal graft were divided into four groups according to the history of acute rejectin(AR) and the concentration of serum creatinine in 6 months(SCr 6mo) after transplantation: Group A and B,having no history of AR with SCr 6mo <130.0umol/L in the formerand ≥130.0 umol/L in the latter,and groups C and D having the history of AR with SCr 6mo <130.0umol/L in the formerand ≥130.0 umol/L in the latter. All groups had the same immunosuppressive protocol.

Results 10th day after operation in groups A and C maintained,while the serum creatinine level in group B and D were obviosly elevated,which was correlated with acute tubular necrosis(ATN), IgA nephritis,donor's age,postoperative hypotention,AR times and the dosage of cyclosporine A.The one– and three-year survival rate of renal graft in group D was significantly lower than groups A,B and C.

Conclusion Acute tubular necrosis was the commonest cause for renal graft dysfunction after renal transplanation.The damage to the kidney in the process of renal removal, ischemia-reperfusion and high dose of cyclosporine A at early stage might affect the recovery of the early renal function.The dysfunction of early renal dysfunction after operation would affect the renal graft long-term survival in patients having AR in 6 months after operation.

INTRODUCTION

With the advent and extensive application of new potent immunosuppressive agents, short-term graft survival has improved substantially in renal transplant recipients, longterm graft survival has not improved over the last decades [1,2,3,4]. An early graft dysfunction has still remained a major long-term clinical problem in renal transplantation[5,6]. Several factors affects renal function immediately after transplantation. Although experimental studies have shown the crucial role of ischemia–reperfusion injury in early graft dysfunction, the relative contribution of donor- or recipient related factors to the development of graft dysfunction is still debated. This study have investigated the correlative factors for early graft dysfunction after renal transplantation and the effects on long-term graft suvival.

MATERIALS AND METHODS

Patients Between January 1,2004 and June 30,201,Two hundred and sixty-one primary cadaver renal transplants were performed in recipients >18 years old at the Jinling Hospital, we eliminated 10 early graft losses due to technical failure from this analysis. Recipient demographics of the study population(n=251) and listed in table 1.

Immunosuppression All recipients had the same immunosuppressive protocal[7].Briefly,all patients received induction immunosuppression immediately after the transplant consisting of prednisone (Pred.), mycophenolate mofetil (MMF), cyclosporine(CsA) or tacrolimus(FK506) When the serum creatinine reached a level of 222.0 umol/L or lower, patients were started on calcineurin inhibitors(CNIs) and then were maintained chronically on Pred, MMF. The dose of CsA was adjusted by CsA though concentrations of 200-400ug/L up to month 4 and at 80-200ug/L thereafter. The dose of FK506 was adjusted by FK506 though concentrations of 6-8 ug/L up to month 4 and at 4-5ug/L thereafter.

Diagosis and treatment of rejection All episodes of acute rejection(AR) were diagnosed on an elevation of serum creatinine and pathologic evidence of rejection by Banff's classification[8].Rejection episodes (all biopsy prevon) were treated by introvenously steroid pulse therapy(methylprednisolone and 500mg/day,for 3 days). Histologically severe rejections and all steroid-resistant rejections were treated with a 7- to 10-day course of rabbit antithymocyte globulin(ATG,100mg/day, v.d.).

Graft monitoring Monitoring of 10 days and 6 months after renal transplantation serum creatinine level changes. Early graft dysfunction was defined as serum creatinine evaluated at 10 days(SCr_{10d}) after transplantation[9]. Dialysis was performed as needed in the posttransplant period, according to the patients clinical status and laboratory parameters. Delayed graft function(DGF) was defined as the need for at least one dialysis session during the first 7 days after transplant[10]. The return of a patient to dialysis,on a

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permanent bases,was considered to be an allograft failure. Graft survival was censered at the time of patient death.

Statistical analyses Survival times were calculated from a life table using the product-limit method. Pairwise evaluated of means and proportions was performed with the t test and chi-square test as appropriate.

RESULTS

Patient characteristics The period of follow up was 3.5 years and by study design,all patients were alive and maintained allograft function for at least 6 months after the treatment. During this period of time,recipient characteristics of the study and listed in table 2. In these studies(Table 3), patients were divided into four groups according to (1) history of AR during the first 6 months after transplantation,and (2) concentration of serum creatinine at 6 months after transplantation ($SCr_{6mo.}$ < or ≥130.0 umol/L).

Correlative factors of the early graft dysfunction Table 4 displays the donor and recipient characteristics and the function of the allograft immediately after the transplant in these four groups of patients. As can be seen, there were no significant differences among these groups in recipient age,cold ischemia time and level of CDC. SCr level at 10th day after opration in groups A and C maintaince normal, while recipients with an elevated SCr_{10d} (Groupa B and D) had received kidneys from older donors,were more likely to be the donor of IgA nephropathy,and also were heavier than patients with a SCr_{10d} <130.0 umol/L. Furthermore,a significantly higher percentage of patients in group D required dialysis after the transplant compared with the other groups of patients.

Predictive value of a SCr_{10d} after transplantation Based on this observation(Table 5),we investigated the implications of the SCr_{10d} concentrations for graft prognosis. Howover,an elevated SCr_{10d} correlated with other potential risk factors for graft survival including:donor's age,IgA nephritis and hypotension during operation; and posttransplantation factors such as acute tubular necrosis(ATN),acute rejection and the dosage of CsA.

Relationship between acute rejection and early graft dysfunction The data shown above may suggest that in patients with acute rejection and elevated SCr_{6mo} (group D) the allograft dysfunction preceded the AR episode,because these patients already had an elevated SCr_{10d} after transplant.Group D showed the relationship between the occurrence of AR and the elevation in serum creatinine concentration. In 68% of tese patients,the serum creatinine was higher at 6 months after transplantation ,after AR, than at 10 days after transplantation(SCr_{10d} 159.1±88.6umol/L,SCr_{6mo} 265.2±102.6umol/L,respectively,P<0.0001). In contrast,3 2% of group D patients had a SCr_{10d} that was greater than or equal to the SCr_{6mo} (283.1±107.5umol/L and 211.4±94.1umol/L) indicating that in these patients renal allograft dysfunction preceded the AR episodes.

Graft survival Graft survival for patients in groups A and B did not differ significantly(Fig.1). It should be noted that plots describing graft survival in these two groups of patients are superimposable during the first 3 years after the transplant but tend to diverge beyond that point. Graft suvival was also not significantly different between patients in group A and C. In contrast,the one– and three-year survival rate of renal graft in group D was significantly lower than groups A,B and C.

DISCUSSION

These studies suggest that the association between decreased early graft function and shortened graft survival is due to associations between the early allograft dysfunction and the pre-transplant and post-transplant risk factors[12]. ATN was the commonest cause for renal graft dysfunction after renal transplanation[13]. The damage to the kidney in the process of renal removal, ischemia-reperfusion and high dose of cyclosporine A at early stage might affect the recovery of the early renal function[14]. Shu-Ming JI et al[11] suggested clinical features of the recipients which received from donor kidney with glomerular mesangial proliferation and marked diffuse granular IgA deposition: edema, proteinuria, microhematuria, hypoalbuminemia, hypertension, and delayed graft function. The presence of IgA deposits on donated kidney, by a possible increase of the immunogenicity of these kidneys, might be a cause of increased rejection.

The SCr_{10d} is an indicator of risk factors from both the donor and recipient,and an elevated SCr_{10d} predicts a higher risk of acquiring additional risk factors early transplantation. Patients with an elevated SCr_{10d} here a higher risk of AR than patients with lower SCr_{10d} and this observation is consistent with othor studies demonstrating a correlation between early allograft damaged and risk for rejection. The reason for this relationship is not entirely clear but several explantations can be suggested. Experimaental and clinical studies have shown that early allograft amage may alter antigenic expression and cytokine production by graft cells that predispose to AR[15,16]. In addition,as show here,patients with elevated Scr_{10d} receive less CsA early after transplantation than patients with lower Scr_{10d}.This finding most likely indicates that patients with reduced renal function are particularly susceptible to the nephrotoxic effects of CsA,which limits the amount of drug that these patients can recieve. It is indeed possible thatt the use of lower dose of CsA in patients with elevated SCr_{10d} places these patients at a higher risk for AR and indeed previous studies noted a relationship between CsA levels during the first few months after transplantation, risk of AR,and allograft survival.

In conclusion, the dysfunction of early renal function after operation would affect the renal graft long- term survival in patients having AR in 6 months after operation. Graft dysfunction predicts poor graft survival only when associated with AR. Similarly, AR predicts a poor renal allograft survival only when associated with graft dysfunction.

Table 1. Recipient demographics(n=251)

Male/female	155/96
Mean age at transplantation SD(yr.)	38.6±15.1
Cold ischemia time (hr.)	21.5±7.8
CDC* (%)	6.7±1.6
PRA* (%)	25.7±10.8

*CDC:complement dependent cytotoxity,PRA:panel reaction antibody

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Table 2.Recipient characteristics of the study for at least 6 months after transplantation

Outcome	n	%
SCr_{10d} ↑	72	28.7
Donor IgA nephropathy [11]	31	12.4
Hypotention during operation	27	10.8
DGF	31	12.4
acute rejection	46	18.3
SCr_{6mo} ↑	63	25.1
Patients died	18	7.2
Graft lost	19	7.6

Table 3.Classification of patients according to the episodes of acute rejection during the first 6 mo. of transplantation and the concentration of SCr_{6mo}.

Groups	n(%)	Acute rejection (mean±SD)	SCr_{6mo}. (umol/L,mean±SD)
A	170(67.7)	No	< 130.0(92.6±16.5)
B	35(13.9)	No	≥ 130.0(203.3±26.5)
C	18(7.1)	Yes(1.2± 0.5)	< 130.0(112.5±21.4)
D	28(11.2)	Yes(1.9± 1.0)	≥ 130.0(256.4±10.6)

Table 4. Pretransplant and early posttansplant variables in patients classified according to acute rejection number and SCr_{6mo}.

Relative factors	Group A (n=170)	Group B (n=35)	Group C (n=18)	Group D (n=28)	*P* Value
Donor					
Age(years)	23.6±2.3	38.7±2.2*	24.1±2.4	24.9±3.6	<0.001[a]
Hot ischemia time (min)	6.3±1.9	6.4±1.9	6.1±1.6	6.0±1.7	>0.05
Cold ischemia time(hr)	20.6±6.8	20.8±5.6	21.1±7.3	20.3±7.1	>0.05
IgA nephropathy(%)	2(1.2)	18(51.4)*	5(27.8)	6(21.4)	<0.05[a]
Recipient					
Age(years)	36.3±5.4	38.1±5.1	39.2±6.3	38.9±5.4	>0.05
Gender(man,%)	100(58.8)	28(80.0)**	10(55.6)	17(60.7)	<0.001[a]
CDC [1] (%)	6.3±1.3	6.8±1.4	6.2±1.3	6.4±1.4	>0.05
PRA [2] (%)	15.3±4.9	16.7±5.1	25.7±7.8*	29.8±8.9*	<0.001[e]
Hypotention in OP.[3](%)	2(1.2)	14(40.0)*	1(5.6)	10(35.7)*	<0.001[b]
Early posttransplant					
Scr_{10d} (umol/L)	132.6±53.0	215.5±109.8*	159.1±88.9	274.0±105.6*	<0.001[b]
DGF [4] (%)	2(1.2)	15(42.9)*	5(27.8)	9(32.1)*	<0.005[b]
ATN [5](%)	2(1.2)	7(20.0)*	1(5.6)	3(10.7)*	<0.01[b]
AR [6]> 1 ☆ (%)	0	0	5(27.8)	15(53.6)*	<0.01[b]
ACR[7] (%)	0	0	14(77.8)*	5(17.9)	<0.001[c]
AVR[8] (%)	0	0	4(22.2)	23(82.1)*	<0.001[d]

a:Group B v.s other groups; b:Group B and Group D v.s Group A and Group C; c: Group D v.s Group C; d: Group C v.s Group D; e: Group C, Group Dv.s Group A, Group B.

[1]CDC: complement dependent cytotoxicity; [2]PRA: panel reactive antibodies; [3] OP:operation; [4] DGF:depayed graft function; [5] ATN:acute tubular necrosis; [6] AR:acute rejection; [7] ACR:acute cellular rejection;[8] AVR:acute vascular rejection

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Table 5. The relationships between the SCr $_{10d}$ and pre-,posttransplant variables

Pretransplant SCr $_{10d}$ r value	P value		Posttransplant SCr $_{10d}$ r value	P value
Donor age (>40yr.)	0.1701	< 0.0001	ATN	0.1309	< 0.0001
Cold ischemia time	0.5621	>0.05	First rejection	0.1703	< 0.0001
Donor IgA nephropathy	0.2120	< 0.001	CsA dosage	- 0.2646	< 0.001
Hypotention during op.	0.2112	< 0.001	Scr $_{6mo}$	0.4728	< 0.0001

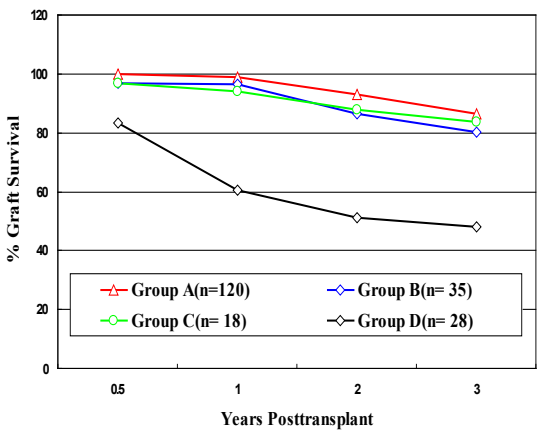

Figure1. Graft survival for patients in the groups

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