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Nifedipine improves immediate, and 6- and 12-month graft function in cyclosporin A (CyA) treated renal allograft recipients

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Abstract. To investigate the effect of oral nifedipine, a calcium channel blocker known not to modify cyclosporin A (CyA) pharmacokinetics, on immediate transplant function and CyA nephrotoxicity, 68 adult renal transplant recipients were pre-operatively randomized to one of three regimes: A (high-dose CyA, initial dose 17 mg/kg per day, maintenance dose 7 mg/kg per day); B (regime A plus oral nifedipine); C low-dose CyA, initial dose 10 mg/kg per day, maintenance 4 mg/kg per day plus azathioprine 1 mg/kg per day). All three groups received identical steroid regimes. Calcium channel blockers of all types were avoided in groups A and C. Delayed graft function (dialysis dependence by day 4) was seen least frequently in group B ($P < 0.02$). Group B had improved graft function at 6 months compared with group A, identified by differences in serum creatinine ($P < 0.05$), GFR ($P < 0.01$) and ERPF ($P < 0.05$). Similar differences in serum creatinine ($P < 0.05$) and GFR ($P < 0.05$) were also identified at 12 months. Group C also had better 6- and 12-month GFR values than group A ($P < 0.05$ each). The three groups did not differ in donor or recipient age, HLA matching, ischaemic or anastomosis times, frequency of early rejection or whole-blood CyA levels. These results indicate that nifedipine significantly improves immediate and medium-term graft function.

Key words: Renal transplantation – Nifedipine – Calcium channel blockers – Cyclosporin A

The introduction of cyclosporin A (CyA) to solid organ transplantation was associated with significantly improved graft survival rates [1, 5], but its nephrotoxicity remains a major clinical disadvantage.

Although the most common clinical manifestation of CyA nephrotoxicity is an acute reversible impairment of renal function [5], CyA has also been linked with an increase in delayed initial graft function [1], presumably due to its exacerbation of renal ischaemic injury [16]. In the longer term, a chronic irreversible nephropathy may occur, characterized by a progressive elevation in serum creatinine [13, 14] and diffuse interstitial fibrosis [15]. The pathophysiology of chronic CyA nephropathy is controversial, but there is mounting evidence that vasoconstriction of the afferent glomerular arteriole is the primary abnormality.

There is evidence from retrospective clinical data and experimental studies in animal models that calcium channel blockers may minimize short- and long-term CyA nephrotoxicity [6, 7, 11, 12]. Calcium channel blockers effect a reduction in calcium influx by their action on voltage-dependent slow calcium channels, thereby reducing intracellular calcium ion accumulation, well recognized as a mediator of ischaemic cell injury [2, 18]. Studies in both cardiac and renal ischaemia suggest that calcium channel blockade prior to any ischaemic insult is required for maximum benefit [2, 18]. The capacity of calcium channel blockers to facilitate vascular smooth muscle relaxation, particularly in the afferent glomerular arteriole [9], may be beneficial in chronic CyA nephrotoxicity.

Although the calcium channel blockers verapamil and diltiazem have been shown to be beneficial in CyA-treated renal transplant recipients [3, 20], they are known to modify CyA pharmacokinetics [4], which may cause difficulty in effective control of CyA therapy.

This prospective study was therefore designed using the calcium channel blocker, nifedipine, which does not modify CyA metabolism [4, 10], to investigate whether administration of oral nifedipine could reduce the incidence of delayed graft function and minimize long-term graft deterioration in renal allograft recipients receiving CyA.

Methods

Subjects

Adult cadaver renal allograft recipients ($n = 68$) were randomized pre-operatively to one of three regimes: *A*, CyA, initial dose of 17 mg/kg per day reduced in a stepwise manner by 2 mg/kg per week

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Table 1. Frequency of delayed initial function in the three study groups

Treatment regime	Number of patients	Incidence (%)
A (High dose CyA)	9/21	43
B (High dose CyA + nifedipine)	2/24	8.3*
C (Triple therapy)	7/23	30.4

* $P < 0.02$

Table 2. Results of serum creatinine, glomerular filtration rate and effective renal plasma flow in the three study groups

	Group A	Group B	Group C
Serum creatinine (μmol/l)			
7 days	394 ± 63	253 ± 58	410 ± 58
28 days	260 ± 40	172 ± 20*	217 ± 34
1 month	206 ± 18	153 ± 11*	166 ± 20
6 months	204 ± 20	155 ± 10*	173 ± 27
12 months	224 ± 23	156 ± 9*	191 ± 28
GFR,(ml/min per 1.73 m^2)			
1 month	47 ± 3.9	45 ± 3.3	52 ± 4.1
6 months	32 ± 3.9	45 ± 2.9**	44 ± 3.2*
12 months	28 ± 4.7	43 ± 3.3*	41 ± 4.1*
ERPF (ml/min per 1.73^2)			
1 month	216 ± 13	183 ± 14	191 ± 36
6 months	239 ± 20	237 ± 15*	204 ± 14
12 months	266 ± 23	222 ± 13	184 ± 14

* $P < 0.05$; ** $P < 0.01$ (groups B or C compared with A)

to a maintenance dose of 7 mg/kg per day at 6 weeks; *B*, CyA as in regime A plus oral nifedipine retard 10 mg three times daily for 1 week, then 20 mg twice daily, increasing to 40 mg twice daily if indicated for hypertension; *C*, CyA, initial dose 10 mg/kg per day reducing by 1 mg/kg per week to a maintenance dose of 4 mg/kg per day at 6 weeks. To achieve effective immunosuppression, group C also received azathioprine at a dose of 1 mg/kg per day. All three groups received identical prednisolone regimes. Calcium channel blockers of all types were avoided in groups A and C and other antihypertensive agents were used if clinically indicated.

CyA was given as gelatin capsules in divided doses thrice daily for 2 weeks after transplantation then twice daily. CyA dosage was based on pretransplant dry weight. Half the daily dose was given orally preoperatively, and individuals randomized to group B received the first dose of oral nifedipine at that time.

Highly sensitized individuals (> 50% panel reactive antibodies) or those receiving an HLA-identical live related graft were excluded from randomization. Other factors which may have modified immediate or long-term graft function were documented: donor and recipient age, ischaemic times, anastomosis times, whole-blood CyA levels (days 0–7), antibody status and blood pressure control.

Trough CyA levels were measured in whole blood by high performance liquid chromatography.

Graft function parameters

Delayed initial function was defined as dialysis dependence by the fourth postoperative day in the absence of graft rejection.

Formal investigation of graft function was performed at 1, 6 and 12 months by measurements of serum creatinine concentration and isotopic assessment of glomerular filtration rate (GFR) (^{51}Cr-EDTA) and effective renal plasma flow (ERPF) (^{131}I-hippuran) using a 'single shot' technique.

Statistics

Statistical analysis was performed with unpaired *t*-tests, Mann Whitney *U* and Chi-squared analysis. Data are presented as mean ± standard error of the mean.

Results

Initial graft function

Delayed initial function was seen least frequently in group B in which 2 of 24 patients (8.3%) were dialysis-dependent by day 4, compared with 9 of 21 in group A (43%), and 7 of 23 in group C (30%) ($P < 0.02$, Chis-quared) (Table 1).

Graft function up to one year

Serum creatinine. Mean serum creatinine concentrations were significantly lower in group B compared with group A at 1, 6 and 12 months ($P < 0.05$) (Table 2, Fig. 1).
Glomerular filtration rate. GFR values for group B were higher than for group A at 6 ($P < 0.01$) and 12 months ($P < 0.05$). Group C showed similar improvements in comparison with group A at both 6 and 12 months ($P < 0.05$) (Table 2, Fig. 2).
Effective renal plasma flow. ERPF was significantly better at 6 months in group B than in group A ($P < 0.05$). There was no significant difference in any graft function parameter at any time point between groups B and C (Table 2, Fig. 3).

There were no significant differences between the three groups in donor or recipient age, HLA mismatches, ischaemic or anastomosis times, mean arterial blood pressure (at any time point), or trough (12-h) whole-blood CyA levels during the first post-transplant week, except at

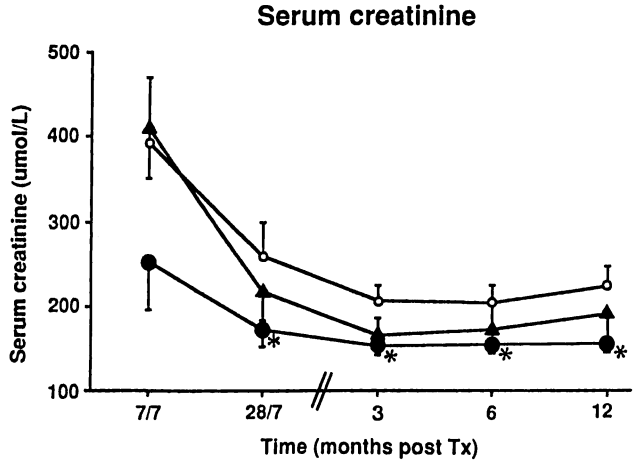

Fig. 1. Serum creatinine concentration during 12 months follow up. ○, group A; ●, group B; ▲, group C

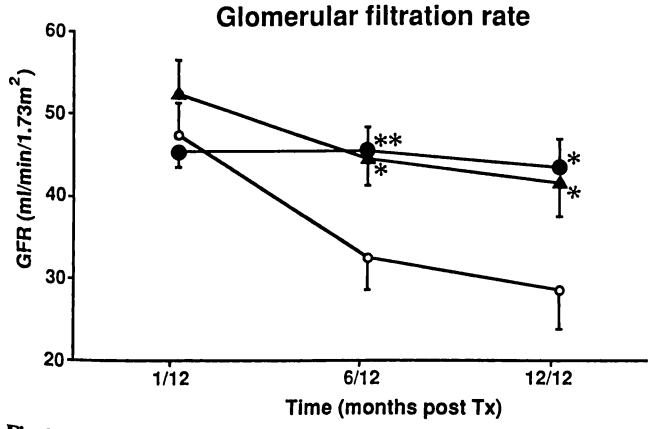

Fig. 2. Glomerular filtration rate during 12 months follow up. ○, group A; ●, group B; ▲, group C

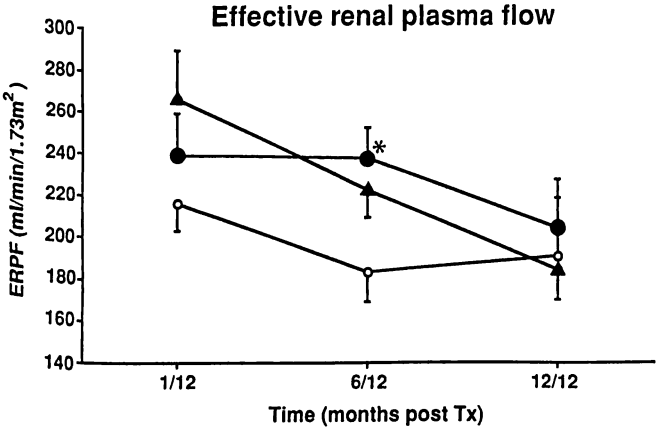

Fig. 3. Effective renal plasma flow during 12 months follow up. ○, group A; ●, group B; ▲, group C

one time point (day 4) when trough levels for group C were significantly lower than those of group A. Documented rejection episodes did not differ in the three groups. However, group B had a significantly higher mean panel reactive antibody status than group A ($P < 0.02$).

Discussion

This study suggests two beneficial effects of nifedipine in renal transplantation using CyA. First, it reduces the incidence of delayed initial function, and second it improves graft function up to 12 months after transplantation. There is a growing body of evidence relating to the beneficial short- and long-term effects of different calcium channel blockers in the context of CyA-treated human renal allograft recipients.

This study supports previous studies of early graft function. The calcium channel blockers diltiazem and verapamil when added to perfusion fluids at organ retrieval and administered to graft recipients have been shown to significantly improve early renal allograft function [3, 20]. Both drugs have the disadvantage of interfering with CyA pharmacokinetics, resulting in unpredictably (30–110%) elevated blood levels [4], and high CyA levels have themselves been associated with delayed graft function [7]. We have demonstrated that preoperative oral nifedipine is a simple method of achieving improved initial graft function without the need for uniformity in organ perfusion, which is difficult to achieve while multicentre organ sharing is practised.

The longer-term benefit of calcium channel blockade has previously been suggested by retrospective studies [6, 19]. These reports have presented graft survival data, or relied on serum creatinine concentration or clearance parameters derived from it, to assess graft function. Serum creatinine is a relatively insensitive measurement of graft function and may be particularly unreliable in patients taking CyA [17]. The present randomized study makes a prospective assessment of graft function using proven isotope reference methods for measurement of GFR and ERPF. With a limited follow-up period of 1 year, no significant differences in graft survival were found, but significant benefits in serum creatinine, GFR and ERPF were found if nifedipine was added to CyA.

Delayed initial function has been associated with poor graft outcome so improved function in established grafts may reflect the late consequence of early non-function. However, the benefits of nifedipine are still present if the data are reanalysed using only those with immediate graft function.

This study demonstrates the benefits of nifedipine in patients on a CyA regime which uses larger doses than preferred by some workers. The data thus far do not show any advantage of the nifedipine regime compared with a triple regime using a lower dose of CyA without nifedipine. Further follow-up of this cohort of patients will, however, provide additional evidence of the impact of nifedipine on longer-term graft function and graft survival.

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