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Verapamil (VP) improves the outcome after renal transplantation (CRT)

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Calcium antagonists (CATs) have a role in the management of certain types of renal insufficiency [6, 15]. These include prophylaxis against post-transplant-associated acute renal failure and cyclosporine A (CsA)-induced renal dysfunction. For the transplanted kidney, CATs may be beneficial in several settings. First, a CAT during organ procurement protects the kidney during ischemic periods [9]. Second, CATs given perioperatively protect the kidney during reperfusion and early after transplantation [2]. Third, CATs also offer protection against CsA nephrotoxicity [1].

Key words: Renal transplantation – Verapamil

Methods

Two prospective randomized clinical studies [1, 2] and one retrospective study were performed [10]. Immunosuppression included 375 mg methylprednisolone on day 1, tapered to 20 mg/day by day 10. Azathioprine, initially 100 mg on day 1 decreased to 25 mg/day for 5 days. Antilymphocyte globulin (14 mg/kg) overlapped with CsA on day 6 (7 mg/kg) and day 7 (12 mg/kg). Verapamil (VP) was initiated on day 3 (study 1), or given into the renal artery (study 2) and continued for 14 days as an oral dose of 120 mg twice daily. Doppler ultrasonography was used to determine blood flow velocities in the renal subcapsular parenchyma. Kidney function was assessed from serum creatinine and glomerular filtration rate (GFR) on days 1 and 7, using subcutaneous ^{125}I-iothalamate [5].

Results

Graft survival

Patients in study 2 have been followed for a mean of 18 months with a current GS for VP patients of 90% (27/30), greater than that for the control patients (68%, (18/29) ($P < 0.01$). These differences were also confirmed in an actuarial graft survival analysis for all patients ($P < 0.0237$) (Fig. 1). The greatest benefits seem to occur with repeat transplants where only one of ten VP treated patiens lost the graft early. In contrast, three of eight control kidneys were still functioning at 1 year ($P < 0.05$). Since July 1990, all CRT recipients at our transplant center have been receiving perioperative treatment with VP. Figure 1 also includes the actuarial survival curve (as of 16 September 1991) for this group of patients ($n = 53$). The tick marks on the lines indicate the follow-up time for each patient with a surviving graft. The 89% actuarial 1-year kidney graft survival estimate in these patients is similar to the 93% rate among the study 2 patients randomized to VP treatment. Eight simultaneous kidney/pancreas transplants were included in this analysis of 53 CRT recipients.

In the retrospective study in which 17 patients received a CAT for treatment of hypertension, graft survival at one year was 93% versus 78% for 23 patients who did not receive a CAT [10].

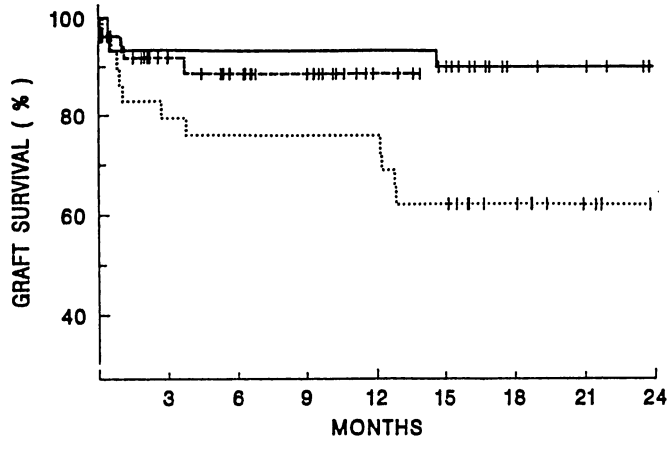

Fig. 1. Actuarial graft survival was significantly improved in 30 patients treated with verapamil *(solid line)* compared with 29 control recipients *(dotted line)* ($P < 0.01$). Currently, 53 kidney recipients receiving perioperative verapamil have an 89% actuarial graft survival *(interrupted line)*

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Rejection episodes

In study 1 of 40 patients, only 3 of 22 patients randomized to VP were treated for a rejection episode within 1 month of transplantation. This was in sharp contrast to 10 of 18 of the control patients treated for rejection ($P < 0.01$) [1]. In the retrospective study, CAT-treated patients had significantly fewer (35%) first rejection episodes during the 1 year follow-up, in contrast to 83% in patients who did not receive a CAT ($P < 0.01$) [10].

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CsA blood levels and CATs

CsA blood levels were about two times higher in patients reveiving VP compared with controls in both studies [1, 2].

CATs and protection from ischemia

When VP was given intra-arterially during surgery (study 2), serum creatinine values on days 1 and 2 after transplantation were significantly lower compared with control patients. With VP serum creatinine fell by 2.7 mg% between days 1 and 2 in contrast to 1.3 mg% for the control patients. On the second day after transplantation creatinine values were 7.4 and 5.6 mg% for control and VP patients, respectively ($P < 0.01$) [2]. By day 7, the majority of patients (77%) receiving VP had serum creatinine values below 2.0 mg% versus only 26% of control patients ($P < 0.01$). Accordingly, on day one GFR was 35 and 19 ml/min for VP and control patients, respectively. By day 7, GFR had increased to 49 and 28 ml/min for VP and control patients ($P < 0.01$).

CATs and CsA nephrotoxicity

Despite the higher CsA blood levels during VP treatment (study 1), serum creatinine levels at 1 week were lower with VP (1.08 ± 0.41 mg%) than those of control patients (1.46 ± 0.46 mg%) ($P < 0.008$). Also the increase in GFR from day 1 to day 7 was greater with VP (32 ± 13 ml/min) compared with 18 ± 13 ml/min in control patients ($P < 0.002$) [1].

Renal blood flow and CATs

CsA-induced blood flow inhibition in animals [13, 14] was later confirmed in CRT recipients where mean diastolic blood flow velocity in ten patients decreased from 10 to 3 cm/s. Despite continued CsA administration, blood flow returned to pre-CsA levels within 3–4 days [14]. Pretreatment with VP prevented this fall in renal blood flow [1]. When VP was given intra-arterially, blood flow was significantly better on the first postoperative day [2]. Only 8% (2/25) of the VP patients had parenchymal blood flow velocity less than 8 cm/s versus 54% of the no-CAT patients ($P < 0.01$).

Discussion

These clinical studies demonstrate several significant benefits from perioperative use of VP in CRTs. Most importantly, graft survival and kidney function were improved. This is further supported by the fact that these results have been corroborated by a current 96% kidney graft survival in CRT recipients with VP given perioperatively (unpublished data). The beneficial effects from CATs may be due to several actions of CATs occurring separately or in combination.

The decreased incidence of acute rejection episodes may be related to the blockage of cellular calcium influx which inhibits lymphocyte activation and macrophage proliferation, both in animal and human in vitro systems [4, 16]. At least part of the beneficial effect of VP on transplant outcome may be due to the increased CsA immunosuppressive effect without accompanying nephrotoxicity because of the increased blood CsA level. Although CATs have complex and incompletely understood interactions with CsA metabolism, both diltiazem and VP compete with CsA for the cytochrome P-450 pathway [9, 12]. In contrast to these two CATs, the dihydropyridine CAT nifedipine does not increase CsA blood concentration [3].

Previously, we demonstrated by in vivo fluorescence microscopy in mice that VP prevents CsA-induced decrease in renal blood flow [13, 14]. Subsequently, these data were confirmed in the clinical setting in CRT recipients [1, 2]. The relative importance of cytoprotection from CATs and their preferential vasodilatation of the afferent arterioles is hard to distinguish. Experimental and clinical data suggest that both mechanisms contribute.

The present studies strongly support routine perioperative use of CATs in CRTs to improve renal function and graft survival. Although VP produces higher CsA blood levels, acute nephrotoxicity is less common and CsA doses are not empirically lowered. Better immunosuppression from increased CsA levels without toxicity probably plays a role in the improved results. Some investigators have steadily reduced the CsA dose to minimize cost [8]. Routine decreases in CsA dose, based on CsA blood levels, may have played a role in the lack of benefits of a CAT in other studies [11]. Based on the results in our two clinical studies the argument could be made not to reduce the CsA dose, but rather accept higher CsA blood levels without nephrotoxicity and gain from increased immunosuppression. Bet-

ter renal function and graft survival vastly outweigh the small monetary gain from decreased CsA dosing.

In summary, VP restores and maintains renal blood flow and minimizes renal injury associated with organ procurement and cold ischemia. The randomized clinical studies confirm our previous animal research that VP prevents CsA-associated deterioration of renal blood flow. VP-treated patients have improved renal blood flow and improved renal function, despite elevated CsA blood levels. VP given intraoperatively, under adequate blood volume expansion, into the renal artery also reduces the need for postoperative hemodialysis. VP-treated patients have fewer rejection episodes, and most importantly VP is associated with improved graft survival.

The beneficial effect of VP on renal transplant outcome may be related to cytoprotection from ischemia, the preferential vasodilatation of the preglomerular arterioles, elevated blood CsA levels and inherent immunosuppressive properties.

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