Pathogenesis of Delayed Kidney Graft Function: Role of Endothelin-1, Thromboxane B_2, and Leukotriene B_4

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DELAYED FUNCTIONING renal allografts (DFGs) have more acute rejection episodes, a lower long-term survival, and increased health care costs as compared to primary functioning grafts (PFGs). In previous studies we found that recipient pretreatment with a single dose of cyclooxygenase or thromboxane and lipoxygenase inhibitors increased graft survival and improved graft function in experimental preservation,[1,2] indicating the role of vasoactive lipid mediators in delayed graft function. Furthermore, recipient pretreatment with acetylsalicylic acid decreased the incidence of delayed graft function and shortened the hospital stay in clinical transplantation.[3] To improve further the timing of application of cyclooxygenase inhibitors, we studied the time course of release of eicosanoid mediators like thromboxane B_2 (TxB_2), 11-dehydro-TxB_2, and leukotrine B_4 (LTB_4) as well as endothelin-1 (ET-1) in a prospective clinical study.

MATERIALS AND METHODS

After approval by the local ethical committee, a consecutive series of 16 patients undergoing renal transplantation were included in the study and separated in two groups according to graft function. group A, patients with PFG (n = 12); and group B, DFG (n = 4). DFG was defined as persistent creatinine elevation posttransplant requiring hemodialysis. Blood and urine samples were taken daily throughout the hospital stay. TxB_2, 11-dehydro-TxB_2, LTB_4, and ET-1 were measured with commercially available enzyme-linked immunosorbent assays (ELISAs) (Eicosanoid ELISA from Cascade Biochemicals, England; ET-1 from Immundiagnostik, Weinheim, Germany) after extraction of mediators from serum and urine samples taken during the first 4 days posttransplant.

RESULTS

The postoperative time course of serum eicosanoid levels is given in Table 1. There was no significant difference between TxB_2, 11-dehydro-TxB_2, and LTB_4 levels in patients with DGF and PGF measured on days 1 through 4 posttransplant even though the levels tended to be higher during days 1 and 2 in patients with DGF. 11-Dehydro-TxB_2 and LTB_4 levels varied considerably in patients with DGF as well as in patients PGF. ET-1 levels are higher in DGF during days 1 and 2 but return to levels comparable to DFG from day 3 on.

DISCUSSION

Our own studies in ischemically damaged kidney slices demonstrated that arachidonic acid is released from cell membranes into the surrounding media,[5] and other studies demonstrated that thrombocytes in patients with chronic renal failure have a lower threshold for thromboxane production on external stimuli. We therefore hypothesised that arachidonic acid is released from cold-stored grafts and metabolized to thromboxane by circulating thrombocytes. Subsequent studies in experimental renal preservation indicated recipient pretreatment with various eicosanoid inhibitors to be beneficial in terms of posttransplant graft function and prevention of acute tubular necrosis.[1,2] Early clinical trials with that approach showed that recipient pretreatment with acetylsalicylic acid significantly decreased DGF and decreased thromboxane concentrations in the renal vein as early as 1 minute after reperfusion.[3] Accumulation of vasoconstrictive substances like endothelin and thromboxane even during cold storage of kidneys

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Table 1. Serum Concentrations of TxB_2, 11-dehydro-TxB_2, LTB_4, and ET-1 (Serum and Urine) During Days 1 Through 4 Posttransplant (Mean ± SE)

Day		1	2	3	4
TxB_2	DGF	2750 ± 320	2500 ± 205	1840 ± 685	2580 ± 230
(pg/mL)	PF	1550 ± 715	1700 ± 600	1675 ± 580	2000 ± 710
LTB_4	DGF	3050 ± 2900	6950 ± 2050	4100 ± 900	5500 ± 1450
(pg/mL)	PF	1600 ± 440	1225 ± 350	2440 ± 850	6140 ± 3340
11-dehydro-TxB_2	DGF	252 ± 249	180 ± 163	2.9 ± 2.3	4.7 ± 1.9
(pg/mL)	PF	17.1 ± 12.5	58 ± 30	152 ± 151	29 ± 25
Serum endothelin	DGF	29.4 ± 2.0	21.8 ± 7.3	31.7 ± 5.1	26.9 ± 2.7
(fmol/mL)	PF	21.1 ± 4.8	18.3 ± 3.5	19.1 ± 4.2	23.9 ± 4.3
Urine endothelin	DGF	5.1 ± 2.1	6.2 ± 1.4	4.3 ± 0.8	4.9 ± 3
(fmol/mL)	PF	3 ± 1.2	4.2 ± 1.4	4.1 ± 0.6	4.2 ± 0.5

was demonstrated by Gianello et al.[4] Thus we performed a clinical trial to study the time course of serum and urine concentrations of eicosanoids and other vasoconstrictive substances, like ET-1, in patients with DGF and PGF. During days 1 and 2 posttransplant, TxB_2, 11-dehydro-TxB_2, and LTB_4 as well as ET-1 showed a trend to be higher in serum of patients with DGF. That difference was not significant, and there was a remarkable interindividual difference in vasoconstrictor concentrations most pronounced for LTB_4 and 11-dehydro-TxB_2. In a previous study we demonstrated[3] that eicosanoid levels in serum of renal allograft patients drop to less than 50% within 10 minutes of reperfusion. We therefore conclude that interventions aimed against the deleterious effects of vasoconstrictive substances released from renal allografts have to start as early as possible in the course of transplantation, preferably before reperfusion, to allow for sufficient binding of antagonists and enzyme inhibitors to their receptor sites. Single-dose or short-term treatment of the recipient with those inhibitors might be sufficient to diminish the vasoconstrictant effects of TxB_2, 11-dehydro-TxB_2, LTB_4, and ET-1.

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