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Effect of prostaglandin E_1 on graft function of kidneys from living related donors

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Abstract. Prostaglandin E_1 (PGE_1) was used in renal transplant recipients with living related donors. The drug was given intravenously from day 1 to day 7 after transplantation at a dose of 40 μg/kg twice a day. A total of 45 patients were studied divided into two groups: 25 patients were treated with PGE_1 (group B) and the remaining 20 patients did not receive the drug (group A). In group B, 24-h creatinine clearance (Ccr) was 66 ± 12.8 ml/min compared with 40.3 ± 13.4 ml/min in group A on the fifth postoperative day ($P < 0.05$). Urinary levels of *N*-acetyl-β-D-glucosaminidase (NAG) and serum levels of platelet factor 4 (PF4) in group B were significantly lower than in group A. On the fourth postoperative day, the urinary excretion of thromboxan B_2 (TxB_2) in group A was higher than in group B, but not significantly (5.1 ± 3.0 ng/day and 2.8 ± 1.1 ng/day, respectively). Acute rejection occurred in four patients in group B and in 10 patients (40%) in group A. The percentage of Leu2a-positive lymphocytes in group B was higher than in group A. We conclude that postoperative administration of PGE_1 improves graft function in kidneys from living related donors.

Key words: Renal transplantation – Prostaglandin E_1 – Doppler ultrasound – Reperfusion injury – Thromboxan B_2 – Lymphocyte subset

Recently, it has been demonstrated that eicosanoids have a beneficial effect on prevention of ischaemic damage and on graft preservation. Current investigations have demonstrated the potent cytoprotective effect of PGE_1 against various types of organ damage. There is, however, little information concerning the effect of this agent in clinical renal transplantation. In a prospective trial conducted in 1990, we gave PGE_1 to renal transplant patients, and also evaluated the effects of PGE_1 on renal allografts from living related donors. We determined graft blood flow, platelet activity, prostaglandin metabolism and immunosuppressive effects.

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Patients and methods

From April 1990 to December 1990, 80 patients were transplanted in our unit for chronic renal failure. To investigate the usefulness of PGE_1, we selected 45 patients randomly and divided them into two groups: 25 patients were treated with PGE_1 (group B) and the remaining 20 patients were not treated with the drug (group A). The proportion of immunological high responders in group A was 54%, and in group B was 57% (Table 1). Transplantation using living related donors was performed in all patients who were then treated with cyclosporin A (CyA), azathioprine (Aza) and methylprednisolone (MP) according to our previously reported protocol. Double filtration plasmapheresis (DFPP) and immunoabsorption methods were performed before transplantation in ABO-incompatible patients.

Administration of PGE_1

During the operation, PGE_1 was administered intravenously at a dose of 20 μg/kg. After the operation PGE_1 was infused intravenously twice daily for 7 postoperative days at a dose of 40 μg/kg.

The parameters studied were peripheral blood count, serum urea, creatinine (Cr), electrolytes, platelet factor 4 (PF4), β-Throm-

Table 1. Comparison between the PGE_1 treatment group and the non-treated control group. There were no significant differences in the donor creatinine clearances, total ischaemic times or graft weights

	PGE_1 group	Control group
Number of cases	20	25
Age (years)	36.7 (25–49)	35.9 (19–52)
Sex (M/F)	12/8	16/9
Type of transplantation		
ABO incompatible	5	4
ABO mismatch	2	2
HLA, AB mismatch		
$\geqslant 3$	3	4
$\leqslant 2$	16	19
MLC stimulation index		
$\geqslant 20$	8	9
$\geqslant 10$	0	6
$\leqslant 10$	8	9
Immunological high responders	11 (57%)	13 (54%)

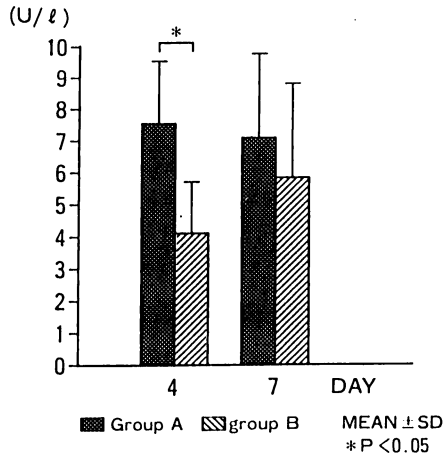

Fig. 1. Urinary NAC levels

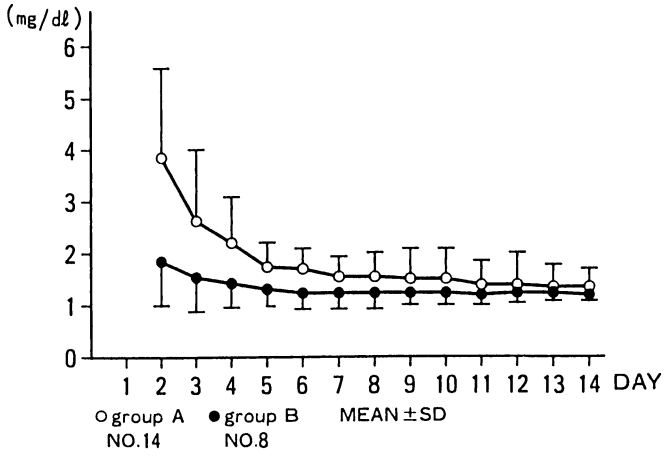

Fig. 2. Changes in the serum creatinine levels. Serum creatinine in group B was decreased more rapidly than in group A, especially in the early postoperative days

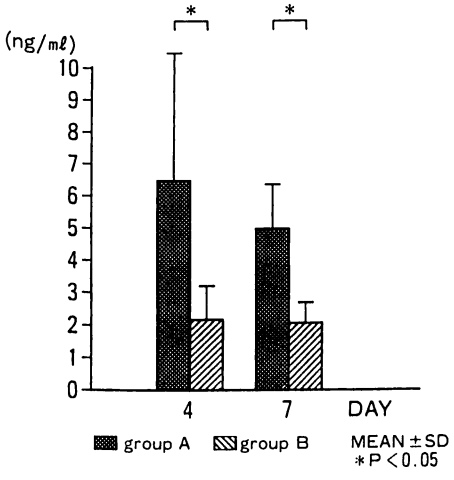

Fig. 3. Serum PF4 levels

boglobuline (β-TG), lymphocyte subset, IgG, IgA, IgM, C3 and C4, and urinary *N*-acetyl-β-D-glucosaminidase (NAG) and prostaglandin metabolites. The levels of serum PF4, serum β-TG and urinary prostaglandin metabolites were analysed by specific radioimmunoassay. For cases of acute rejection, values were excluded restrospectively from 3 days before the onset of acute rejection.

Doppler ultrasound was used to obtain blood flow velocity curves from the interlobular artery of the transplanted renal allograft. The Doppler flow pattern was observed using a colour Doppler ultrasound scanner SSD680 (Aloka, Japan). The peak systolic velocity (PSV), end diastolic velocity (EDV), average velocity (AGV), pulsatility index (PI) and resistive index (RI) were measured from the interlobular artery of the renal allograft. These parameters were measured at two to four points on the artery and an average was taken.

Statistical analyses

All values are presented as mean ± SD and were analysed by Student's *t*-test. *P*-values less than 0.05 were considered to be significant.

Results

The numbers of patients available for study on each postoperative day are shown in Table 2.

Function of renal allograft

The 24-h Ccr values were 42.4 ± 18.9, 40.3 ± 13.5 and 46.1 ± 14.2 ml/min on days 3, 5 and 7, respectively, in group A, and 70.3 ± 20.5, 66.0 ± 12.8 ($P < 0.05$) and 73.2 ± 12.7 ($P < 0.05$) on days 3, 5 and 7 in group B. Urine volume and urine levels of electrolytes were the same in both groups. Levels of urine NAG in group A were 7.6 ± 2.9 U/l on day 4 and 7.1 ± 2.8 U/l on the day-7, and in group B were 4.2 ± 2.2 U/l on day 4 and 6.1 ± 3.7 U/l day 7 (Fig. 1). A dramatic decrease in serum creatinine level was observed in group B after the first 4 days after transplantation, but after 7 days the serum creatinine level was the same as in group A (Fig. 2).

Platelet activity

Serum PF4 level was 6.5 ± 4.9 ng/ml in group A and 2.2 ± 0.87 ng/ml in group B on day 4 ($P < 0.05$) and 5.0 ± 1.4 ng/ml in group A and 2.1 ± 0.7 ng/ml in group B on day 7 ($P < 0.05$) (Fig. 3).

On postoperative day 7, serum β-TG levels were 77.8 ± 26.3 ng/ml in group A and 42.7 ± 4.65 ng/ml in group B ($P < 0.05$).

Urine prostaglandin metabolites

Urinary levels of TxB_2 were 5.1 ± 3.0 ng/day in group A and 2.8 ± 1.1 ng/day in group B, and of 6-keto-$PGF_1\alpha$ were 3.8 ± 1.8 ng/day in group A and 3.6 ± 1.4 ng/day in

Table 2. The numbers of patients available for study on each operative day

	Day					
	1	2	3	4	5	7
Group A	19	18	17	16	15	13
Group B	21	20	17	15	13	11

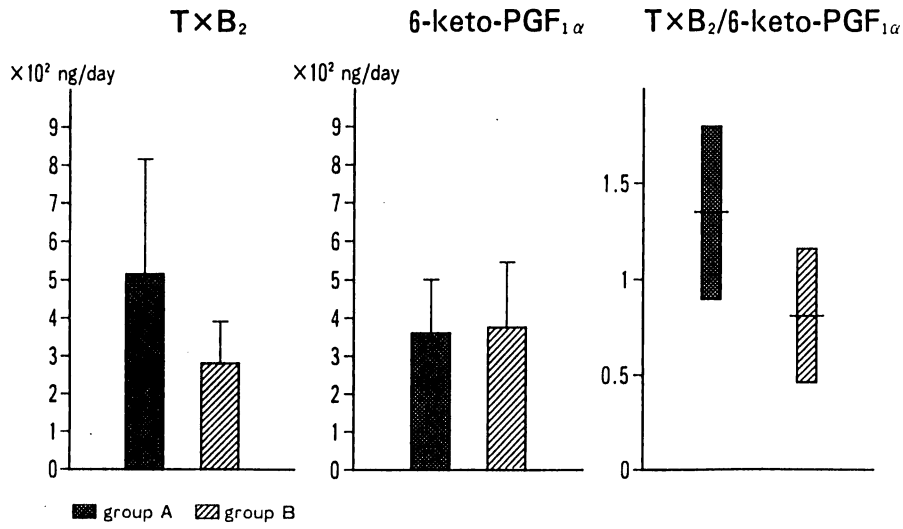

Fig. 4. The levels of urine TxB_2, 6-keto-$PGF_{1\alpha}$ and TxB_2/6-keto-$PGF_{1\alpha}$ on the fourth postoperative day

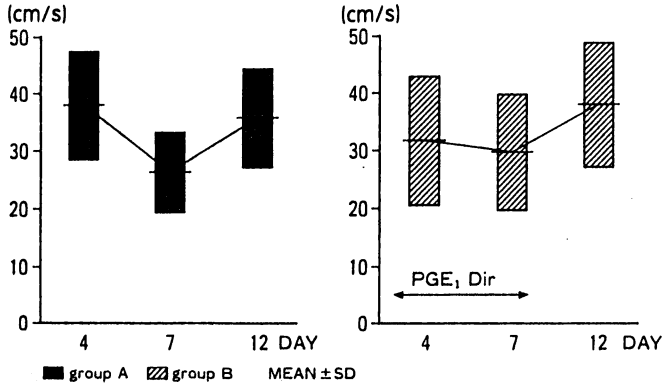

Fig. 5. Changes in PSV after transplantation. The doppler ultrasound method was used to obtain blood flow velocity curves from the interlobular artery of the transplanted renal allografts. We measured the velocity curve on the same artery of each the renal allograft. The average PSV decreased in the group A but not significantly in the group B

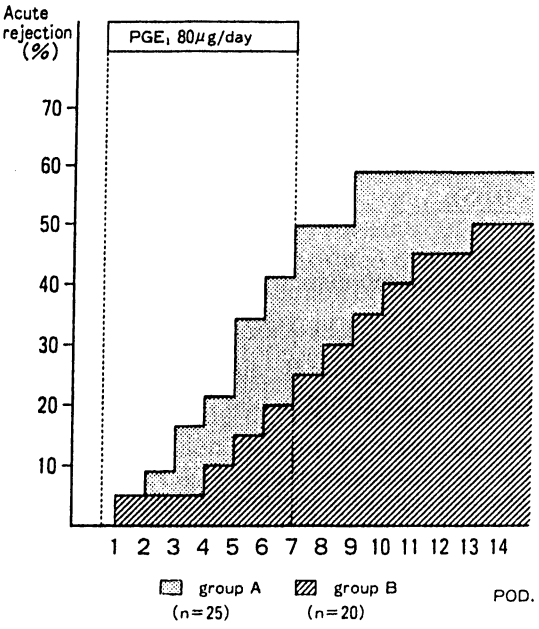

Fig. 6. The proportion of patients with acute rejection on each postoperative day

group B on postoperative day 4. The urinary levels of TxB_2 and TxB_2/6-keto-$PGF_1\alpha$ of group A were higher than those of group B (Fig. 4).

Blood flow in renal allografts

PSV, EDV, RI and PI were measured by Doppler ultrasound methods from the interlobular artery of the renal allograft. RI and PI were increasing at the time of acute rejection in each group, but no difference was observed between the two groups at the time of rejection. Figure 5 shows the changes in PSV that were measured at the time of no rejection following in 2 weeks. PSV measured on day 7 was slightly decreased in group A but showed no change in group B, but the difference between the groups was not significant.

Acute rejection and immunological follow up

The combined rate of acute rejection (AR) from day 1 to day 7 was 40% in group A and 20% in group B. After stopping the infusion of PGE_1 in group B, the number of patients with acute rejection increased and the overall rate of AR was 50% 2 weeks after surgery (Fig. 6). Figure 7 shows the T-cell subsets in the peripheral blood of the patients in whom AR occurred 3 days later. The percentage of Leu2a-positive lymphocytes was $22.2 \pm 3.7\%$ in group A and $34.5 \pm 7.5\%$ in group B ($P < 0.05$). The Leu3a to Leu2a ratio was 2.5 ± 0.4 in group A and 1.4 ± 0.5 in group B. Serum levels of C3, C4, IgG, IgA and IgM were not significantly different between the two groups.

Discussion

PGE_1 possibly protects the renal allograft from ischaemia reperfusion injury by increasing the capillary blood flow and by an immunosupressive effect.

In the PGE_1 group, the 24-h Ccr levels were higher than those in the non-treatment group for 7 postoperative days. Urinary NAG levels in the non-treatment group were

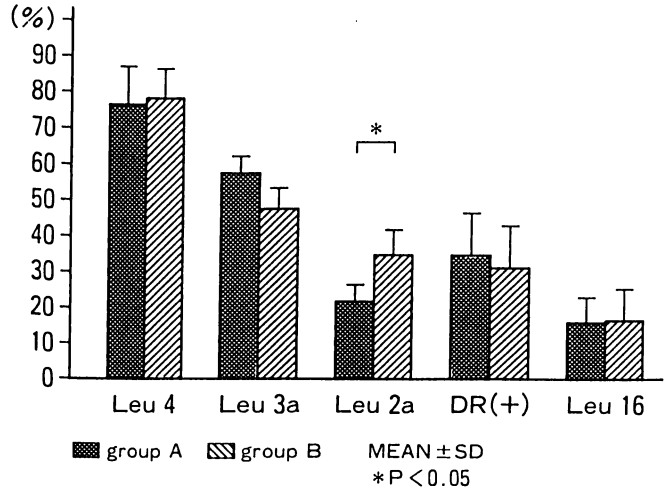

Fig. 7. Lymphocyte subsets on the fourth postoperative day

higher than those of the PGE_1 group. It is well known that NAG is included in the lysosome of renal tubular cells. The leakage of hydrolytic enzymes from lysosomes and their activation by acidosis in the ischaemic kidney seem to be critical contributing factors to irreversible change in cells. The marked suppression of urinary NAG activity observed in this study suggests a stabilizing effect of PGE_1 on the lysosomal membrane in transplanted kidney injured by ischaemia and reperfusion.

It has been reported that serum TxB_2 levels and TxB_2/6-keto-$PGF_1\alpha$ increase after reperfusion of a transplanted organ [2, 3]. It is well known that TxA_2 activates platelet aggregation and prostaglandin I_2 (PGI) inhibits platelet activation. The vasospastic effect of TxA_2 together with the increase in TxB_2/6-keto-$PGF_1\alpha$ decrease organ blood flow and inhibit the peripheral blood supply. Our results demonstrate that the levels of urinary TxB_2, urinary TxB_2/6-keto-$PGF_1\alpha$, serum PF4 and serum β-TG in the PGE_1 group were lower than in the non-treated group. PF4 and β-TG are released from activated platelets. The suppression of urinary excretion of TxB_2 and platelet activation observed in this study suggest that PGE_1 suppresses the production of TxA_2 from platelets and changes the balance of prostaglandins after reperfusion of the renal allograft. We sugest that PGE_1 protects the transplanted kidney from the early ischaemia that occurs immediately after blood reperfusion, and this may be one of the cytoprotective effects of PGE_1 in renal transplantation.

We studied renal allograft blood flow using a Doppler ultrasound blood perfusion monitor. Flow velocity decreased without rejection on days 5–7 in the non-treated group but did not decrease in the PGE_1-treated group. This change in velocity may have been due to tissue oedema or an increase in tissue TxB_2 production, but we did not examine this. On the other hand, there were no differences in the early postoperative state (days 1–4). These results suggest that PGE_1 improves capillary blood flow, which was not measured by Doppler ultrasound methods in the early postoperative days.

It has been reported that PGE_1 induces T-helper cells at low concentrations and T-suppressor cells at high concentrations [7]. The suppression of antigen presentation by macrophages [4, 5, 6], interleukin-1 (IL-1) production by macrophages and IL-2 production by T cells [1] have been demonstrated in an in vivo study. In clinical renal transplantation, there is little information concerning the immunosuppressive effect of PGE_1.

Our results demonstrate a low frequency of acute rejection in the PGE_1-treated group during PGE_1 infusion, and frequent acute rejection after stopping the infusion. During the week after transplantation, the ratio of Leu2a-positive cells in the PGE_1-treated group was higher than in the non-treated group. These results suggest that PGE_1 may suppress cell immunity and modify T-cell differentiation on renal transplantation.

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