A Double-Blind, Randomized, Placebo-Controlled Trial of Prostaglandin E_1 in Liver Transplantation

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A double-blind placebo-controlled trial of intravenous prostaglandin PGE_1 (40 μg/h) was conducted in adult orthotopic liver transplant recipients. Infusion was started intraoperatively and continued for up to 21 days. Patients were followed up for 180 days postoperatively. Among 172 patients eligible for treatment in the study, 160 could be evaluated (78 PGE_1; 82 placebo). Patient and graft survival were similar (PGE_1: 16 deaths, 9 retransplantations [7 survivors]; controls: 15 deaths, 6 retransplantations [3 survivors]). In patients with surviving grafts, however, PGE_1 administration resulted in a 23% shorter mean duration of hospitalization following transplantation (PGE_1: 24.4 days; controls: 31.8 days; P = .02) and a 40% shorter length of time postoperatively in the intensive care unit (PGE_1: 8.2 days; controls 13.7 days; P = .05). Reduced needs for renal support (P = .03) or surgical intervention other than retransplantation (P = .02) were also noted with PGE_1 use. Further, PGE_1 administration resulted in a trend toward improved survival rates in patients with mild renal impairment (preoperative serum creatinine 1.5 mg percent or greater; P = .08). Neither the incidence of acute cellular rejection nor of primary nonfunction was significantly different in the two groups. Phlebitis was the only complication that was more common during PGE_1 administration, (PGE_1: 9; controls: 4). These results suggest that PGE_1 use in hepatic allograft recipients reduces morbidity and may result in sizable cost reductions. (HEPATOLOGY 1995;21:366-372.)

Despite advances in surgical technique, donor-organ preservation, and immediate and long-term allograft management, orthotopic liver transplantation remains fraught with immunologic, physiologic, hemodynamic, and microbiologic problems. Consequently, liver transplantation continues to have a high early morbidity and mortality.[1] Early graft failure frequently leads to retransplantation, which depletes the scarce donor-organ pool and increases costs. Furthermore, early mortality and lengthy hospitalization for postoperative morbidity are associated with the highest charges for orthotopic liver transplantation.[2]

Prostaglandins of the E family have properties suggestive of a potential to improve liver allograft function. A range of inhibitory actions on the cellular immune responses that may characterize acute rejection has been shown with exogenous prostaglandin E (PGE). *In vitro* studies have documented PGE inhibition of murine lymphocyte-mediated cytotoxicity[3] and splenic T-cell-mediated toxicity against target hepatocytes,[4] as well as inhibition of human lymphocyte interleukin-2-driven alloproliferative responses.[5] *In vivo* investigations have shown PGE suppression of acute immune-complex–induced vasculitis and adjuvant-induced polyarthritis in rats[6] and of the immune response in a model of systemic lupus erythematosus in mice.[7]

PGE also has been shown to have an impact on nonimmune actions that may have effects on liver allografts. Investigations have documented *in vitro* changes in human erythrocyte membrane flexibility,[8] increases in canine hepatic blood flow,[9] and changes in the ratio of insulin and glucagon in human serum.[10] More specifically, collagen formation has been shown to be delayed by 16,16-dimethyl PGE_2 in rodent models of hepatic injury from a fibrogenic diet[11,12] and by a PGE_1 analogue in rats that had undergone bile duct ligation.[13]

Furthermore, 16,16-dimethyl PGE_2 has been shown to increase survival by decreasing the level of circulating tumor necrosis factor in rats following endotoxin challenge.[14] PGE analogues also have been shown to protect liver *in situ* and hepatocytes in culture[15] from damage by murine hepatitis virus type 3 and to inhibit hepatic-reperfusion injury or free-radical–mediated liver damage in animal transplantation models.[16,17]

Data from clinical trials suggest that exogenous pros-

Abbreviation: PGE, prostaglandin E_1.

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taglandins may be beneficial in solid-organ transplantations. In a double-blind, placebo-controlled study of oral PGE_1 in renal-transplant recipients, acute graft refection occurred less frequently in the PGE-treated group ($P = .02$).[18] A subsequent study of PGE_2 in renal transplantation, however, did not confirm these observations.[19] In human liver transplantation, a nonrandomized, controlled study showed a reduced number of early liver allograft rejection episodes in PGE_1-treated patients ($P = .003$) in the first 6 weeks following primary orthotopic liver transplantation.[20] In other studies, PGE_1 has been reported to improve liver,[21-23] renal,[24,25] and platelet[26] function and possibly to ameliorate primary nonfunction after orthotopic liver transplantation.[23]

Despite these encouraging data, rigorous controlled clinical trials of prostaglandin agonists in the early postoperative management of orthotopic liver grafts are lacking. We, therefore, initiated a double-blind, randomized, placebo-controlled trial of intravenous PGE_1 in adult orthotopic liver-transplant recipients.

MATERIALS AND METHODS

Patients and Study Design. Between April 20, 1990 and November 3, 1992, all patients aged 18 years or older who were on the liver-transplantation waiting list at the University of Michigan Medical Center were invited to participate. Patients who may have previously been enrolled in the study and who were waiting for retransplantation also were eligible if the first transplantation had been performed at least 180 days earlier. This allowed ample time for the effects of PGE_1, which the patient may have received earlier to dissipate. The study was approved by the institutional review board of the University of Michigan. Informed consent was requested from all eligible patients and was obtained from all those who enrolled. Immediately before transplantation, patients were assigned to receive either PGE_1 or placebo infusion under a randomization code generated by the University of Michigan School of Public Health and kept by the Division of Investigational Pharmacy, University of Michigan Hospitals. PGE_1 (Prostin VR Pediatric) was provided by the Upjohn Company, Kalamazoo, Mich. The infusion was started at a rate of 10 μg/h before the anhepatic phase and was increased by 10 μg/h every 30 minutes until a maintenance level of 40 μg/h had been reached. When the infusion contained PGE_1, this protocol ensured that the newly transplanted organ would be exposed to the drug as soon as the clamps were released. A fresh infusion was prepared every 24 hours, and infusions were continued for up to 21 days. Infusion was stopped for the following reasons: discharge from the hospital, treatment failure caused by primary nonfunction, miscellaneous adverse events, retransplantation, or death. When primary nonfunction occurred, the blind code was maintained although the patient may have been switched to open-label PGE_1 infusion. As a precaution, a physician who was not an investigator under this protocol had access to this randomization code. When 20 patients had been enrolled, and again about midway through the study, he examined the mortality data to determine whether to continue the study.

Normal posttransplantation care routine was maintained during this study. The immunosuppressive regimen included administration of methylprednisolone (initially 200 mg/d and then progressively lower doses), azathioprine 1 mg/kg/d, and antilymphocyte globulin (20 mg/kg for at least 5 days), and cyclosporin A, once renal function had become normal or had stabilized. Cyclosporine was given at an initial oral dose of 14 mg/kg/d. When a therapeutic level (150 ± 25 μg/mL whole blood as measured by high-performance liquid chromatography) had been reached, the antilymphocyte globulin was discontinued. Protocol liver biopsies were performed at 7, 14, and 21 days and additionally as clinically indicated.

Definition of Endpoints. Mortality was defined as death from any cause within 180 days of the transplantation. Morbidity was defined on the basis of time spent in the hospital during the first 180 days after transplantation, time spent in the intensive care unit with or without ventilatory support, and the duration of the initial hospitalization following transplantation.

Complications were categorized as the initiation of artificial renal support (dialysis or continuous arterio-venous hemofiltration), reoperations, reintubation, gastrointestinal bleeding, or major infections. Reoperation was classified as surgical intervention for therapeutic purposes (excluding endoscopic or biopsy procedures, paracentesis, thoracentesis, or the insertion of monitoring equipment). Major infections were defined as isolation of one or more recognized pathogens from blood, serous cavities, or sputum (if accompanied by an infiltrate on chest radiograph), and/or isolation of fungal organisms from any source other than skin, urine, or catheter tip. Gastrointestinal bleeding was defined as bleeding from the gastrointestinal tract requiring transfusion.

Because the benefit of shortened hospital stay cannot be applied to patients who die or require retransplantation, these patients were excluded from analyses of morbidity data as defined above.

Primary nonfunction of the allograft was diagnosed if a patient met at least five of the following criteria: bile output of <20 mL in 24 hours; serum bilirubin greater than 10 mg% and increasing at a rate of at least 5 mg%/d; prothrombin time of 15 seconds or longer; factor V concentration $\leq 25\%$ of normal levels; patency of major vessels demonstrated by Doppler ultrasound; and a clinical picture compatible with primary nonfunction.

The diagnosis of acute cellular rejection was based on the histopathologic criteria of Snover et al.[27] Chronic ductopenic rejection was based on the histopathologic criteria of Ludwig et al.[28]

Statistical Methods. To determine, prospectively, the number of patients required to complete the study, it was postulated that the incidence of acute cellular rejection would need to be lowered from 33%, which was the incidence in our program when the trial was begun, to about 16% and that the duration of hospitalization should be reduced by one third. With a significance level of 5% and a power of 80%, the calculated sample size was 85 patients in each group.

Data were extracted from patients' charts, entered into text files by a professional data-entry firm, and then transferred to a statistical data base. All statistical analyses were performed using SAS software (Statistical Analysis System, Cary, NC).

Comparisons of nominal variables between treatment groups were made by Fisher's exact test.[29] The differences in lengths of various stays (e.g., days in the intensive care unit between treatment groups were evaluated by the Wilcoxon's rank-sum test.[30] All significance values reported are based on two-tailed tests.

RESULTS

Among 172 patients considered for enrollment in the protocol, 2 patients were found to be ineligible because

TABLE 1. Treatment Group Assignment and Mortality Among Patients Who Were Rerandomized and Retransplanted During the Study and Who Were Excluded From Analyses

Treatment Group Assignments	No. of Patients	No. of Survivors of Retransplantation
PGE_1 then PGE_1	2	2
PGE_1 then placebo	1	0
Placebo then PGE_1	4	3
Placebo then placebo	2	1

TABLE 3. Mortality and Retransplantation Within 180 Days Following Liver Transplantation in PGE_1 and Placebo Treatment Groups

Retransplantation Within 180 Days	Mortality	PGE_1	Placebo
No	Alive	53	58
	Dead	16	15
Yes	Alive	7	6
	Dead	2	3
Total	Alive	59	64
	Dead	18	18

of incorrect documentation of the informed consent, and 5 refused randomization. An additional 9 patients were excluded from analyses because they underwent retransplantation and were rerandomized, and retreated within 180 days. The outcomes of the retransplantation operations in these 9 rerandomized patients are shown in Table 1. Four patients underwent retransplantation and were rerandomized into the study after completing 180 days of follow-up; these patients were included as 8 patients in the analyses. The study was terminated and the code was broken on May 11, 1993, after the last enrolled patient had completed 180 days of follow-up.

Among 160 patients analyzed, PGE_1 was administered to 78 patients, and placebo was given to 82 patients. The clinical characteristics of these 160 patients are shown in Table 2, and the outcomes of the transplantation operation after 180 days of follow-up are shown in Table 3. Also, the distribution of known predictors of outcome, such as age or transplantation from the intensive care unit or preoperative renal status (Table 2), did not differ significantly between the two groups. There was no difference in mortality or in the frequency of retransplantation within 180 days between the two groups. The causes of death among those patients who did not undergo retransplantation within 180 days are listed in Table 4.

Nine patients experienced primary graft nonfunction and were then administered open-label PGE_1 infusions (three patients in the PGE_1 group and six control patients: Table 5). An additional three patients (two PGE_1 patients and one control patient) were withdrawn from the protocol (i.e., infusion was halted) by the attending surgeon without their meeting all the criteria for primary nonfunction.

Hospitalization data (Table 6) for the patients with surviving grafts showed that, in comparison with controls, PGE_1-treated patients spent 40% fewer days in the intensive care unit ($P = .05$) and 23% less time in the hospital during the transplant admission ($P = .02$). In addition, the mean number of total days of hospitalization during the first 180 days after surgery was less by 22% for the PGE-treated group than for controls, although the difference between the groups did not achieve significance ($P = .10$).

Analyses of the incidence of major complications indicated that, in comparison with control patients, significantly fewer PGE_1-treated patients required renal support ($P = .03$) or reoperation ($P = .02$) (Table 7). Although reintubations were more frequent among patients in the placebo group than in patients who re-

TABLE 2. Characteristics of Patients Who Completed 180 Days of Follow-Up After Liver Transplantation

Characteristic	PGE_1	Placebo
	(N = 78)	(N = 82)
Mean age in years ± SEM	43.6 ± 1.34	44.9 ± 1.42
Sex M/F	41/37	40/42
Transplanted from ICU	12	14
Diagnosis		
Alcohol-induced cirrhosis	32	27
Hepatitis C	5	7
Cryptogenic cirrhosis	9	15
Primary biliary cirrhosis	8	8
Primary sclerosing cholangitis	5	4
Chronic hepatitis B	2	1
Chronic autoimmune hepatitis	2	5
Fulminant hepatitis	3	3
Chronic hepatitis (B + C)	1	1
Wilson's disease	1	2
Others	10	9

TABLE 4. Causes of Death Among Patients not Receiving Retransplants Within 180 Days Following Liver Transplantation

Cause Of Death	No. of Deaths	
	PGE_1 (N = 53)	Placebo (N = 58)
Multisystem failure	0	4
Intraoperative death	1	3
Primary nonfunction	1	2
Vascular thrombosis	2	1
Sepsis	5	5
Intraabdominal bleeding	1	1
Pulmonary bleeding	0	1
Recurrent liver cancer	0	1
Cardiac failure	1	1
Intracranial hemorrhage	0	1
Total	16	15

TABLE 5. Outcome in Nine Patients With Primary Nonfunction During Infusion With PGE_1 (Three Patients) or Placebo (Six Patients)

Outcome	No. of Patients
Recovery	1*
Death	2
Retransplantation	
Alive	4
Dead	2

* This patient was in the PGE_1-treated group.

ceived PGE_1, the difference between groups was not significant ($P = .08$). The incidences of gastrointestinal bleeding and infections were similar in the two groups. The distribution of the indications for reoperation in the PGE_1-treated group and in the control group is presented in Table 8.

Although mortality among patients with renal failure (serum creatinine ≥ 1.5 mg%) at the time of transplantation was lower in patients treated with PGE_1 than in control patients, the difference between the groups was not significant ($P = .08$) (Table 9).

Liver biopsy showed evidence of acute cellular rejection in 17 of 64 PGE_1-treated patients (26%) and in 28 of 74 placebo-treated patients (38%; $P = .20$). In some instances, death or clinical contraindication precluded the performance liver biopsies. During the period of PGE_1 infusion, acute cellular rejection was diagnosed in 1 patient, and incomplete evidence of rejection (all but one of the criteria for rejection present) was seen in 3 other patients.

Chronic ductopenic rejection was diagnosed in three patients treated with PGE_1, two of whom showed acute cellular rejection on an earlier biopsy, and in five placebo-treated patients, three of whom showed acute cellular rejection on an earlier biopsy.

Events that led to discontinuation of infusion before 21 days are listed in Table 10. These patients received the drug for a mean of 12.6 ± 0.94 (SEM) days. None of the adverse events were severe. Hypotension, gastrointestinal symptoms, and headache did not occur.

Computerized laboratory data were available on all but the first 24 patients. These are summarized in Table 11. The data were similar except for a statistical difference in the serum bilirubin.

One patient deserves comment. This 39-year-old man was identified in the course of review of the intraoperative records to determine the possible mechanism of the PGE effect. He was randomized to receive the drug, and the infusion was prepared and provided by the pharmacy. As he developed hypotension, sufficient to require dopamine, during the induction of anesthesia and before the incision was made, it was elected by the anesthesiologist to remove him from the study. He therefore did not receive PGE_1 at any time. He survived after 31 days of intubation, 48 days in the intensive

TABLE 6. Morbidity in Terms of Time Spent in the Hospital During the Study by Patients Who Completed 180 Days of Follow-Up

Time Period	Mean No. of Days (SEM)		
	PGE_1 (N = 53)	Placebo (N = 58)	*P* Value
In intensive care unit	8.2 (1.3)	13.7 (3.1)	.05
In hospital during transplantation admission	24.4 (3.01)	31.8 (3.9)	.02
In hospital during first 180 postoperative days	32.5 (3.3)	41.5 (4.2)	.10

TABLE 7. Incidence of Major Complications, Excluding Patients Who Died or Who Underwent Retransplantation

Complication	PGE_1 (N = 53)	Placebo (N = 58)	*P* Value
Renal support required	1	8	.03
Reoperations required			
0	43	35	.02
1	9	14	
≥ 2	1	9	
Reintubations			.08
0	50	48	
≥ 1	1	2	
Infections	8	11	.64
Gastrointestinal bleeding	2	2	.61

TABLE 8. Indications for Reoperations in PGE_1 and Placebo Treatment Groups (Excluding Deaths and Retransplants)*

Type of Operation	Specific Operation	PGE_1 (N = 53)	Placebo (N = 58)
Tissue integrity	Wound repair	4	5
	Bile duct repair	1	4
	Splenic varix	0	1
	Extraabdominal aneurysm	0	1
	Lacerated liver	0	1
	Ventral hernia	0	1
	Subtotal	5	13
Ventilatory	Tracheotomy	1	5
	Chest tube	0	3
	Subtotal	1	8
Infection	Abdominal abscess	2	5
	Empyema	0	1
	Axillary abscess	0	1
	Subtotal	2	8
Hemorrhage control	Abdominal	2	7
	Extraperitoneal	0	2
	Subtotal	2	9
Exploratory laparotomy†		2	4
	Total operations	12	42

* Patients may have required more than one reoperation.
† Includes one patient requiring a tracheotomy at operation.

TABLE 9. Mortality During 180 Days Following Transplantation in Patients With Preoperative Serum Creatinine Levels of 1.5 mg% or Greater in PGE_1 and Placebo Treatment Groups

Mortality	PGE_1	Placebo	*P* Value
Alive	17	9	.08
Dead	5	9	

care unit, 103 days during the initial hospitalization and four subsequent admissions, so that he spent 142 of the first 180 days after surgery in the hospital. His course was characterized by three laparotomies, including one in which a tracheotomy was performed. His preoperative creatinine level was 2.5 mg%. He required artificial renal support on two separate occasions during his initial admission for 28 and 29 days, respectively, and had two separate episodes of infection. His liver biopsy specimens did not show conclusive evidence of rejection. Although this patient contributed significantly to the postoperative morbidity of the patients assigned to receive active drug, it was elected to retain him in the study under the intent-to-treat rule.

DISCUSSION

This study reports the mortality and morbidity profile of perioperative PGE_1 infusion in orthotopic liver transplantation. Although neither an effect on mortality nor on the need for retransplantation was shown, other evidence of significant clinical benefit was obtained. Comparisons with placebo infusion showed that PGE_1 administration resulted in decreased morbidity as evidenced by a 23% shorter initial hospital stay and a reduction of 40% in time spent in the intensive care unit. Although a detailed economic analysis is being conducted separately, the present data suggest that PGE_1 administered early in the operative course may significantly reduce the cost of liver transplantation.

In comparison with control patients, the shorter length of initial hospitalization in PGE_1-treated patients may be attributed to the decreased need for postoperative renal support, the lowered incidence of reintubation, and a nonspecific trend toward a reduced need for reoperations over a broad spectrum of indications. In addition, PGE_1 did not increase the incidence of infections or hemorrhagic complications, and the anticipated gastrointestinal symptoms were not seen.

Our data also suggest that patients with high preoperative serum creatinine concentrations ($\geq$1.5 mg%) are more likely to survive liver transplantation when given PGE_1. Previous studies have shown that such patients carry a greater risk of postoperative mortality.[31,32]

The mechanisms by which PGE_1 exerts its effects are not clear. The main benefit of the drug may possibly be based on a hemodynamic, hematologic, or cardiovascular effect rather than on direct action on the allograft. In the present study, PGE_1 had ample time to equilibrate between the circulation and body tissues other than liver before the transplanted organ was placed in circulation. Indeed, use of preservation solution containing prostaglandin for liver preperfusion immediately before release of the clamps may merit evaluation because the fate of the transplanted liver may be determined within seconds of renewed circulation.

Alternatively, PGE_1 may exert its effect via modulation of the immune response because prostaglandins are immunosuppressive mediators.[33] *In vitro* studies in rats indicate that during sepsis prostaglandins may down-regulate the release and consequently the circulating levels of specific cytokines.[34] A preliminary survey of tumor necrosis factor, interleukin-8, interleukin-6, and monocyte chemotactic peptide in the present study population, however, did not suggest that the concentrations in serum of these cytokines were modified by PGE_1 infusion (Kimberly A. Brown, unpublished data).

The effects of PGE_1 on the liver were not striking. In particular, PGE_1 did not significantly decrease the incidence of acute cellular rejection. Acute cellular rejection occurred not only after the PGE_1 infusion had been stopped but even during its administration.

Based on the work of Greig et al,[23] we had hoped that the PGE_1-treated patients would be spared the complication of primary graft nonfunction. We found, however, that PGE_1 did not have significant effect on the incidence of this complication or its outcome. Primary graft nonfunction should be diagnosed by a cluster of clinical and biochemical parameters that may reflect hemodynamic, immunologic, hematologic, and possibly other factors that have not been measured and that may obscure a heterogeneous etiology.

Our earlier studies[35] suggested that biochemical determinations on the transplanted liver are not very sensitive indicators of histopathological changes. Likewise, in this study there were no significant differences in AST, ALT, AP activities, and platelet concentrations at a time when PGE_1 was still being received. The differences in the serum bilirubin concentrations are interesting, but not of striking clinical significance, nor can they be interpreted without additional data.

The lack of a clearly demonstrable effect of PGE_1 on

TABLE 10. Adverse Events Resulting in Early Discontinuation of PGE_1 or Placebo Infusion

Adverse Events	No. of Patients	
	PGE_1	Placebo
Phlebitis	9	4
No reason noted	3	0
Joint pains	1	0
Patient request	0	1
Neurological problems, possibly PGE related	0	2
Sepsis	0	1
Physician judgment	0	1
Incidental cancer noted	0	1
Decreased platelets	0	1
Total	13	11

TABLE 11. Laboratory Data Mean ± 1 SEM (n)

	Bilirubin (mg%)	AST (IU)	ALT (IU)	AP (IU)	PLT × 10^3/mm^3
			Post-Op Day 2		
PGE_1	4.85 ± 0.56 (71)	1,088 ± 178 (71)	990 ± 162 (71)	96.8 ± 8.4 (71)	68.1 ± 6.0 (69)
Placebo	6.95 ± 0.71 (73) $P < .025$	1,520 ± 252 (73)	1,182 ± 185 (73)	109 ± 12.6 (73)	63 ± 23 (73)
			Post-Op Day 10		
PGE_1	5.86 ± 0.76 (61)	106 ± 19 (61)	286 ± 48 (61)	187 ± 13 (61)	131 ± 13 (61)
Placebo	9.49 ± 1.1 (67) $P < .005$	135 ± 27 (67)	296 ± 45 (67)	187 ± 17 (67)	139 ± 16 (67)

the liver may be explained by the relatively low incidence of any complication involving the liver parenchyma in this study. In contrast to our results, a recent study[20] showed a significantly lower incidence of early rejection (within the first 6 weeks following liver transplantation) in patients receiving PGE_1 (55%) compared with patients receiving placebo (80%; $P = .023$).

Further work is needed to determine the mechanism(s) of action of the drug in hepatic allograft recipients and to optimize its use. The latter may require modification of the immunosuppressive protocol, modification of the dose, and/or administration of PGE_1 preoperatively. In the present investigation, PGE_1 lowered the incidence of postoperative renal failure and reduced the likelihood that patients would need to return to the operating room. The observed favorable trends in the incidence of acute cellular rejection and in chronic ductopenic rejection also favor the drug despite the lack of statistical significance in the present trial. Additional studies may further define the role of PGE_1 in the management of hepatic allograft recipients.

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