Effectiveness of Intraportal Prostaglandin E1 Administration After Liver Transplantation


ABSTRACT

Purpose. Prostaglandin E1 (PGE1) has been used to improve hepatic blood flow and to reduce ischemia reperfusion injuries of allografts in liver transplantation. However, PGE1 undergoes extensive metabolic clearance in the pulmonary and splanchnic circulation during intravenous administration. We analyzed the effect of intraportally administered PGE1.

Methods. Sixty living-donor liver transplant recipients received continuous infusions of PGE1 for 10 days immediately after the reperfusion of the allografts. Of them, 40 recipients received PGE1 intravenously (IV group) via the internal jugular vein, and 20 recipients received PGE1 intraportally (IP group) through a catheter in the inferior mesenteric vein. Data were collected for 3 weeks postoperatively.

Results. The IP group exhibited lower initial aspartate aminotransferase and alanine aminotransferase levels compared with the IV group. However, no apparent differences were recognized in the serum albumin, total bilirubin, alkaline phosphatase, r-glutamyl transpeptidase, or prothrombin time levels between the 2 groups. Chylorous ascites were observed more frequently in the IP group. There was no difference in portal venous flow measured by Doppler sonogram between the 2 groups during the first postoperative week.

Conclusion. This study demonstrated that intraportal administration of PGE1 had a better cytoprotective effect against hepatocellular damage than intravenous administration, although it did not have additional benefits for perihepatic hemodynamics.

Prostaglandin E1 (PGE1), an E series prostaglandin, is a prostacyclin analogue. PGE1 has pharmacological activities, including vasodilatation, inhibition of platelet aggregation, activation of fibrinolysis, and inhibitory effects on inflammatory cells, and may modulate cellular proliferation and fibrinogenesis. This latter property of PGE1 has been used for the maintenance of a patent ductus arteriosus in neonates with congenital heart disease and in the treatment of pulmonary hypertension, low cardiac output state, and respiratory distress syndrome. Recently, it has been reported that PGE1 is able to improve hepatic blood flow, to reduce the ischemia reperfusion injury of allografts, and to recover hepatic function in patients with fulminant hepatic failure or primary graft nonfunction after liver transplantation.

However, an important pharmacological consideration in using PGE1 therapeutically is its rapid and extensive metabolism. When PGE1 is delivered intravenously, about 70% of the PGE1 is metabolized in the lung on a single pass and is also used in the intestinal tract. Due to this metabolic inactivation or clearance in the pulmonary and splanchnic circulation during intravenous administration, the concentration of PGE1 reaching the hepatic allograft is much decreased. Therefore, as a target organ infusion protocol, the portal vein is theoretically a better administration route for PGE1 infusion to prevent the extensive first-pass metabolism of PGE1 by the lungs and to maximize the bioavailability and clinical efficacy of PGE1.

In this study, we compared the effects of PGE1 on the allograft function based on the 2 different administration routes.
routes: systemic intravenous administration (IV group) versus intraportal administration (IP group). We also analyzed the effect of intraportally administered PGE1 on hepatic blood flow following liver transplantation.

PATIENTS AND METHODS

Patient Sample
Sixty consecutive adult patients who underwent living-donor liver transplantation at our institution were considered for the study. There were no exclusion criteria.

Immunosuppressive Protocol
Basiliximab (Simultect, Novartis, Switzerland), an anti–interleukin-2R antibody, was administered for immune induction therapy during the intraoperative period and the fourth postoperative day. A standard triple immunosuppressive regimen with a calcineurin inhibitor, mycophenolate, and methylprednisolone was used. All patients received tacrolimus (Prograf, Astellas, Japan) or cyclosporine (Sandimmune, Novartis, Switzerland) as a calcineurin inhibitor. Tacrolimus was started at a dose of 0.5 mg twice daily on the third postoperative day, 2 hours after the administration of mycophenolate. The trough concentration of tacrolimus was monitored daily and doses were adjusted according to the target concentration of 8–10 ng/mL. Cyclosporine was given orally at a dose of 2 mg/kg/d, and was subsequently adjusted to obtain blood levels of 200 to 300 ng/mL. A total of 1.5 g (750 mg twice daily) of mycophenolate (CellCept, Roche, Switzerland) was provided the day after liver transplantation. The mycophenolate dose was adjusted according to the occurrence of hematologic or gastrointestinal side effects. A total of 500 mg of methylprednisolone was injected in all patients during the anhepatic period, followed by 500 mg on the first postoperative day. Thereafter, the drug dosage was gradually tapered to 32 mg/d over a period of 10 days.

Study Design
The recipient operation was performed using standardized techniques. Sixty recipients received a continuous infusion of liposomal PGE1 (Alprostadil, Eglandin, Mitsubishi Tanabe Pharma, Seoul, Korea) immediately after reperfusion of the allograft, provided that their blood pressure was stable. PGE1 was administered as a continuous infusion at a dose of 0.73 µg/kg/h for the first 10 days postoperative using a syringe pump. Forty of the recipients received PGE1 IV (IV group) via an internal jugular vein, and the remaining 20 recipients received PGE1 IP (IP group) through a catheter in the inferior mesenteric vein.

Intraportal PGE1 infusions were performed as follows. A 16-gauge double-lumen antithrombotic catheter was inserted via the inferior mesenteric vein before the recipient’s liver was removed. The tip of the catheter was positioned 1 cm above the porto-splenic confluence and fixed in place by ligation with a rubber band. The other end was drawn outside the body via the surgical wound. The study drug was administered continuously through the catheter during the operation and while patients were in the intensive care unit. We removed the catheter on the tenth day after liver transplantation.

Clinical Follow-Up
Three weeks of postoperative data were collected for each patient. We investigated the incidences of clinical events such as catheter-related complications, changes in perihepatic hemodynamics, and postoperative laboratory parameters. Doppler ultrasonograms were performed every other postoperative day (EOD) in all recipients to confirm the patency of the hepatic vasculature and to estimate the portal venous flow. We measured the mean values of serum albumin, total bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), r-glutamyl transpeptidase (GGT), lactate dehydrogenase (LDH), and serum creatinine daily until the 21st postoperative day. A liver biopsy was conducted if the level of either AST or ALT was increased by >100% as compared with the previous level.

Statistical Analyses
All data were expressed as means ± standard deviations and analyzed using PASW 18.0 software for Windows. Discontinuous data were analyzed using Fisher exact test or two-sample Student t tests, continuous data using repeated measures analysis of variance (ANOVA), and categorical data using chi-square test. P < .05 was considered statistically significant.

RESULTS
Recipient Demographics
There were no significant differences in recipient characteristics between the IV and IP groups. The recipient’s severity of illness at the time of transplantation was also similar in the 2 groups. The details are shown in Table 1. A right lobe graft was performed in 58 cases and the remaining 2 cases were extended right lobe grafts with the middle hepatic vein.

Early Clinical Outcomes
In our study sample, cardiovascular instability as a side effect of PGE1 infusion was not recognized during the observation period. Likewise, primary graft nonfunction was not observed in either group. There were no statistically significant differences between the 2 groups with regard to the pathological results for the allograft biopsy. However, the difference in the incidence of chylous ascites approached statistical significance. Chyloperitoneum was diagnosed when peritoneal drainage contained a high level of triglycerides of >110 mg/dL upon lipoprotein analysis. This was observed more frequently in the IP group (2 of 40 [20%] in the IV group vs 4 of 20 [5%] in the IP group; P = .005). Early clinical outcomes including catheter-related complications are summarized in Table 2. Fatal complications such as portal vein thrombosis did not occur in the IP group.

Perihepatic Hemodynamics
During the first postoperative week, the mean value of portal venous velocity measured using Doppler ultrasound was 93.5 ± 48.1 (median, 80.0) cm/sec in the IV group and 94.7 ± 45.1 (median, 82.0) cm/sec in the IP group. Clinically, increased portal venous flow was demonstrated in both groups after continuous PGE1 infusion. Nevertheless, the IP group did not show a higher increase than that of the IV group. No difference was seen in portal blood flow...
between the 2 groups ($P = .3068$). Thus, the route of PGE1 administration, IV or IP, is not likely to affect perihepatic hemodynamics.

**Laboratory Parameters**

The trends in the mean values of the parameters observed in both the IV and IP groups showed significant increases and decreases in the immediate postoperative periods. However, there were no significant differences in changes over time of serum AST or ALT levels between the IV and IP groups ($P$ values were .485 and .387, respectively). No apparent differences in changes over time were recognized in terms of serum albumin, total bilirubin, ALP, GGT, LDH, or serum creatinine levels between the 2 groups.

Figure 1 shows the posttransplantation change with time of serum albumin, total bilirubin, AST, ALT, ALP, GGT, LDH, and creatinine during the 21 postoperative days in the IV and IP groups.

However, the IP group exhibited lower initial AST and ALT levels on the first posttransplantation day as compared with the IV group (239.4 ± 120.9 IU/L vs 354.6 ± 244.0 IU/L; $P = .029$; 268.1 ± 152.1 IU/L vs 397.3 ± 282.9 IU/L; $P = .017$, respectively). IP PGE1 administration resulted in a significant reduction in initial AST and ALT levels. These results suggested that the IP administration of PGE1 has greater protective effect against hepatocyte damage than does IV administration.

**DISCUSSION**

In experimental models as well as in clinical liver transplantation, PGE1 is reported to reduce hepatic ischemia reperfusion injury after warm ischemia and cold preservation,11-12 to prevent primary allograft nonfunction,5 and to improve hepatic blood flow.13-15 However, because of the metabolic clearance of PGE1 in the pulmonary and splanchnic circulations,2 there is considerable doubt that IV PGE1 is bioavailable in the liver. In practice, randomized trials16-18 of PGE1 infusion during and after liver transplantation have been shown to have no effect on patient and graft survival, rejection, or primary nonfunction.

### Table 1. Recipient Demographics Between the IV Group and IP Group

<table>
<thead>
<tr>
<th></th>
<th>IV Group (n = 40)</th>
<th>IP Group (n = 20)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male:female)</td>
<td>25:15</td>
<td>17:3</td>
<td>.073*</td>
</tr>
<tr>
<td>Mean age (y)</td>
<td>51.2 ± 8.0</td>
<td>48.9 ± 6.7</td>
<td>.269†</td>
</tr>
<tr>
<td>Mean body weight (kg)</td>
<td>68.2 ± 9.1</td>
<td>73.7 ± 12.5</td>
<td>.056‡</td>
</tr>
<tr>
<td>Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute liver failure</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Acute on chronic hepatitis B</td>
<td>2</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis B cirrhosis</td>
<td>10</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Viral hepatitis C cirrhosis</td>
<td>2</td>
<td>1</td>
<td>.109†</td>
</tr>
<tr>
<td>NBNC (cryptogenic) cirrhosis</td>
<td>23</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>1</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Hepatocellular carcinoma (among them)</td>
<td>22</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>CTP score (Child classification A:B:C)</td>
<td>7:13:20</td>
<td>5:2:13</td>
<td>.164*</td>
</tr>
<tr>
<td>MELD score (&lt;25: &gt;25)</td>
<td>31.9</td>
<td>17.3</td>
<td>.549†</td>
</tr>
<tr>
<td>GRWR (&lt;0.8: &gt;0.8)</td>
<td>7:33</td>
<td>5:15</td>
<td>.511†</td>
</tr>
<tr>
<td>GV/SLV (&lt;40%: &gt;40%)</td>
<td>1:39</td>
<td>2:18</td>
<td>.255†</td>
</tr>
<tr>
<td>Macrosteatosis in graft liver (%)</td>
<td>7.2 ± 5.1</td>
<td>7.9 ± 5.1</td>
<td>.428†</td>
</tr>
<tr>
<td>Calcineurin inhibitors (tacrolimus:cyclosporine)</td>
<td>37:3</td>
<td>19:1</td>
<td>1.000†</td>
</tr>
</tbody>
</table>

Abbreviations: NBNC, non-B non-C; CTP, Child Turcotte Pugh; MELD, Model for End-stage Liver Disease; GRWR, graft recipient weight ratio; GV/SLV, graft volume/standard liver volume.

* Chi-square test.
† Fisher exact test.
‡ Two-sample test.

### Table 2. Early Clinical Outcomes Including Catheter-Related Complications in IV and IP Groups

<table>
<thead>
<tr>
<th>Pathology on liver biopsy</th>
<th>IV Group (n = 40)</th>
<th>IP Group (n = 20)</th>
<th>Total (n = 60)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute cellular rejection</td>
<td>2 (5.0%)</td>
<td>0 (0.0%)</td>
<td>2 (3.3%)</td>
<td>.548</td>
</tr>
<tr>
<td>Cholestasis</td>
<td>2 (5.0%)</td>
<td>2 (10.0%)</td>
<td>4 (6.7%)</td>
<td>.595</td>
</tr>
<tr>
<td>Preservation injury</td>
<td>4 (10.0%)</td>
<td>1 (5.0%)</td>
<td>5 (8.3%)</td>
<td>.656</td>
</tr>
<tr>
<td>Postoperative hemoperitoneum</td>
<td>5 (12.5%)</td>
<td>5 (25.0%)</td>
<td>10 (16.7%)</td>
<td>.278</td>
</tr>
<tr>
<td>Postoperative infectious episode</td>
<td>4 (10.0%)</td>
<td>3 (15.0%)</td>
<td>7 (11.7%)</td>
<td>.676</td>
</tr>
<tr>
<td>Need for renal replacement therapy</td>
<td>2 (5.0%)</td>
<td>3 (15.0%)</td>
<td>5 (8.3%)</td>
<td>.322</td>
</tr>
<tr>
<td>Chylous ascites</td>
<td>2 (5.0%)</td>
<td>4 (20.0%)</td>
<td>6 (10.0%)</td>
<td>.005</td>
</tr>
<tr>
<td>Portal vein thrombosis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Fisher exact test.
This pharmacological condition demanded a new approach to PGE1 administration. Aono et al suggested that, in a 66% hepatectomized rat model, the omentum was a better site for PGE1 administration than the vein, and that omental PGE1 delivery was effective. Nakai et al assessed the effectiveness of continuous PGE1 administration into the hepatic artery. Recent studies have suggested that IP administration of PGE1 is more desirable than IV administration for obtaining an effective level in the liver. Both Totsuka et al and Inagaki et al demonstrated the superiority of IP infusion to IV infusion against warm ischemic liver damage. They confirmed that IP administered PGE1 improved the hepatic microcirculation and stabilized the hepatocellular membrane.

As mentioned above, IP PGE1 infusion exerted greater cytoprotective effects compared with IV PGE1 infusion, judging from the significant reduction in the level of serum transaminases on the first posttransplantation day. Several investigators agreed that IP administered PGE1 provided better cytoprotection, although the mechanism was not completely understood. Hossain et al observed a less severe extent of portal venous congestion and sinusoidal congestion in an IP PGE1 group by histopathologic examination of the liver tissue after reperfusion. Hafez et al advocated that IP PGE1 directly protected sinusoidal endothelial cells through tumor necrosis factor-α suppression. Iwata et al hypothesized that the cytoprotective effect of IP PGE1 was attributable to the reduction of leukocyte-endothelial cell adhesion by selective suppression of intercellular adhesion molecule-1 expression on the endothelium.

During the study period, a total of 4 (20%) cases of chyloperitoneum occurred in the IP group. We hypothesized that these resulted from operative injuries to the abdominal lymphatics around the inferior mesenteric vein during the procedures for catheter insertion. These complications were not serious at an output rate of <500 mL per day, so they were treated conservatively and resolved spontaneously after their observation. We only provided a low-fat diet. All cases recovered within 1 week of nonoperative management, and there were no other complications related to the catheters except for chylous ascites.

Although some reports noted that PGE1 improved hepatic blood flow, in fact, the precise effect of the IP infusion of PGE1 on hepatic blood flow was not known. Kawachi et al demonstrated that the IP infusion of PGE1 improved hepatic allograft blood flow by affecting hepatic arterial flow, not portal venous flow, and suggested that IP PGE1 might improve graft viability after liver transplantation. Nakai et al verified that hepatic hemodynamics and oxygen metabolism did not change during the administration of PGE1 into the portal vein. In our study, we observed no augmenting effect on portal venous flow in recipients in whom PGE1 was administered IP compared with those who received it IV, which is consistent with the above reports. In addition, changes in serum enzymes and bilirubin were not significantly different over time between the 2 groups. These results were similar to the study that showed no differences in the biochemical parameters when PGE1 was administered IP in a dog model of hepatic ischemia following reperfusion.

In conclusion, we demonstrated that the IP infused PGE1 reduced liver injury, which was proved by the reduction in initial serum transaminases after liver transplantation. Our results suggest that IP administration of PGE1 has greater cytoprotective effect against hepatocellular damage than IV.
administration, although it did not result in additional benefits for perihepatic hemodynamics.

REFERENCES