Appraisal of Intra-Arterial Infusion of Prostaglandin E₁ in Patients Undergoing Major Hepatic Resection — Report of Four Cases

Tsutomu Sato, Ouki Yasui, Toshiaki Kurokawa, Yoshihiro Asanuma and Kenji Koyama

Department of Surgery, Akita University School of Medicine, Akita 010–8543

Sato, T., Yasui, O., Kurokawa, T., Asanuma, Y. and Koyama, K. Appraisal of Intra-Arterial Infusion of Prostaglandin E₁ in Patients Undergoing Major Hepatic Resection — Report of Four Cases. Tohoku J. Exp. Med., 2001, 195(2), 125–133 — In order to reduce risk for postoperative acute liver failure, prostaglandin E₁ (PGE₁) was administered either from the hepatic artery (HA) or the superior mesenteric artery (SMA) in four high-risk cases undergoing major hepatic resection. Two cases were subjected to HA PGE₁ infusion for 3 or 4 days after surgery at a rate of 0.01 μg/kg/min. Both patients had hepatocellular carcinoma (HCC) associated with chronic hepatitis, and ICG R₁₅ was 17.6% and 14.5%, respectively. Right hemihepatectomy and extended right hemihepatectomy were performed. Serum total bilirubin (T. Bil.) peak value was 2.2 mg/100 ml in Case 1 and 2.1 mg/100 ml in Case 2. In Case 1, decreased bile flow was observed immediately after cessation of PGE₁. The other two cases were subjected to SMA PGE₁ infusion for 5 or 6 days after surgery at the same rate. In Case 3, right hemihepatectomy was performed for HCC on a cirrhotic liver four weeks after right portal vein embolization, in which preoperative ICG R₁₅ was 19.0%. Peak T. Bil level was 3.7 mg/100 ml with uneventful postoperative course. In Case 4 with a huge cholangioma, right trisegmentectomy was performed. Peak serum T. Bil level was 1.7 mg/100 ml in this uneventful postoperative course. In Case 3 and Case 4, portal blood flow, measured by Doppler ultrasonography, was markedly increased by PGE₁ infusion. From these results, intraarterial PGE₁ infusion might be useful in prevention of postoperative liver failure after major hepatic resection. —— postoperative acute liver failure; prostaglandin E₁; portal blood flow

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Address for reprints: Kenji Koyama, M.D., FACS, Department of Surgery, Akita University School of Medicine, 1–1–1 Hondo, Akita 010–8543, Japan.
E-mail: koyama@surgl.med.akita-u.ac.jp
Postoperative acute liver failure following liver resection is a serious and often fatal complication, especially when it occurs in a liver with chronic liver disease (Detroz et al. 1994). The most efficient method of postoperative liver failure prevention is to restrict patients with poor hepatic functional reserve from being liver resection candidates, while choosing a precisely appropriate operative procedure for the individual patient’s liver function (Noguchi et al. 1990; Makuuchi et al. 1993; Yamanaka et al. 1994). Actually, such an appraisal of liver functional reserve has played an important role in increasing safety in liver surgery for patients with chronic liver disease during the last several decades (Riordan and Williams 1998). However, better results can not be achieved for patients with poor liver function while such patients are excluded from surgical indications. Therefore, another breakthrough must be made to raise the safety level of liver resection and improve long-term survival rates after liver resection.

In fact, prostaglandin E\(_1\) (PGE\(_1\)) has attracted attention for its various protective effects against liver injury (Mizoguchi et al. 1987; Sinclair et al. 1989). Efficacy of PGE\(_1\) has also been reported in liver resection and transplantation clinical settings (Greig et al. 1989; Baek et al. 1999). Still, approximately 70% of PGE\(_1\) is inactivated during a single passage through the lung (Golub et al. 1975). Therefore, direct infusion of this drug into the liver bloodstream might be more beneficial than systemic intravenous (iv) infusion. This can be achieved either via the portal vein (Totsuka et al. 1995; Kawachi et al. 1997) or via the hepatic artery (HA) (Nakai et al. 1998; Sato et al. 2000a). Comparing these two methods, HA infusion of PGE\(_1\) can increase liver blood flow and hepatic oxygen delivery while intraportal infusion does not affect hepatic hemodynamics. Another potential option to deliver PGE\(_1\) to the liver is administration from the superior mesenteric artery (SMA). This method might have two advantages: one is increased portal blood flow (Sato et al. 2000b); the other is more efficient delivery of PGE\(_1\) to the liver than by iv infusion.

Given this situation, in order to increase the safety of major hepatic resection, either HA infusion or SMA infusion of PGE\(_1\) was performed in three hepatocellular carcinoma (HCC) patients and one cholangiocellular carcinoma (CCC) patient undergoing major hepatic resection with certain risks. Based on clinical courses and outcomes of these four cases as well as the authors’ basic backgrounds of animal experimentation, efficacy of intra-arterial PGE\(_1\) infusion is discussed.

**CASE REPORTS**

**Case 1**

A 49-year-old man was admitted to Akita University Medical Center with diagnosed HCC complicated by chronic hepatitis (hepatitis C). Abdominal CT scan showed a tumor with 7 cm maximal diameter in the liver right lobe. The tumor invaded extensively into the right portal and right hepatic veins, with tumor thrombi extending as far as the inferior vena cava (IVC) orifice to the right atrium. Table 1 shows preoperative liver function test results of the four presented cases in this report. Among these, ICG R\(_{15}\) was 17.6% and the k value was 0.122 (0.5 mg/kg dye) in Case 1. Oral glucose tolerance test (o-GTT) (75 g) showed a diabetic pattern according to classification of the Japanese Diabetes Mellitus (DM) Study Group.

Right hemihepatectomy was performed by the controlled method (Raven 1949) through a serial celio-thoracotomy. Tumor thrombi from the right hepatic caval confluence to the IVC was resected under total hepatic vascular exclusion (THVE) (Yamaoka et al. 1992) without bypass for 30 minutes. Operating time was 10 hours and intraoperative blood loss was 2000 ml. During liver parenchyma resection, continuous infusion of PGE\(_1\) (Alprostadil, Ono Pharmaceuticals, Osaka) was started at a rate of 0.01
Table 1. Results of preoperative liver function tests

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Case 1</th>
<th>Case 2</th>
<th>Case 3</th>
<th>Case 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, Sex</td>
<td>49, male</td>
<td>69, male</td>
<td>62, male</td>
<td>59, male</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>HCC</td>
<td>HCC</td>
<td>HCC</td>
<td>CCC</td>
</tr>
<tr>
<td>Liver disease</td>
<td>Chronic hepatitis</td>
<td>Chronic hepatitis</td>
<td>Liver cirrhosis</td>
<td>None</td>
</tr>
<tr>
<td>AST/ALT (IU/liter)</td>
<td>84/66</td>
<td>20/30</td>
<td>20/16</td>
<td>56/38</td>
</tr>
<tr>
<td>Total bilirubin (mg/100 ml)</td>
<td>1.1</td>
<td>1.0</td>
<td>0.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Albumin (g/100 ml)</td>
<td>4.2</td>
<td>4.3</td>
<td>4.2</td>
<td>4.5</td>
</tr>
<tr>
<td>Prothrombin time (%)</td>
<td>86</td>
<td>54</td>
<td>72</td>
<td>100</td>
</tr>
<tr>
<td>Platelet count (/mm³)</td>
<td>96 000</td>
<td>290 000</td>
<td>250 000</td>
<td>291 000</td>
</tr>
<tr>
<td>ICG R₁₃ (0.5 mg/kg)</td>
<td>17.6%</td>
<td>14.5%</td>
<td>19.0%</td>
<td>6.8%</td>
</tr>
<tr>
<td>ICG k (0.5 mg/kg)</td>
<td>0.122</td>
<td>0.124</td>
<td>0.103</td>
<td>0.168</td>
</tr>
<tr>
<td>75 g o-GTT</td>
<td>DM pattern</td>
<td>DM pattern</td>
<td>DM pattern</td>
<td>Not done</td>
</tr>
<tr>
<td>Other surgical risk</td>
<td>None</td>
<td>Heart, arrhythmia</td>
<td>None</td>
<td>None</td>
</tr>
</tbody>
</table>

μg/kg/min from the HA, in which a heparin-coated catheter had been inserted prior to the operation. This patient's PGE₁ infusion was discontinued on postoperative day (POD) 5.

Postoperative liver function is shown in Fig. 1. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) peak levels were 448 IU/liter and 495 IU/liter, respectively, on POD 2. Serum T. Bil. peak value was 2.2 mg/100 ml on POD 1. Bile flow from the external biliary drainage tube inserted from the cystic duct was from 170 ml to 200 ml/day during PGE₁ infusion. After PGE₁ infusion cessation, bile flow decreased to between 95 ml
and 100 ml/day. The patient was discharged on POD 46 after intra-arterial chemotherapy from the HA.

**Case 2**

The patient was a 69-year-old man with a 10 cm diameter tumor in the right lobe and a portion of the medial segment. He had no chronic liver disease history and serological viral markers were negative. Serum AST and ALT were within normal ranges, but ICG R\textsubscript{15} was 14.5% and the k value was 0.124. The patient had a history of DM for decades, necessitating insulin treatment, and he had undergone aortic valve replacement 10 years previously. Heart function was not good. The ejection fraction of his heart was estimated at 0.41 with ultrasonography (US) and multifocal ventricular premature contractions appeared in the electrocardiogram.

An extended right hemihepatectomy was performed by the controlled method under celiotomy. Intraoperative blood loss was 1200 ml and the operating time was 4.5 hours. As in Case 1, continuous PGE\textsubscript{1} infusion from the HA at the same rate as Case 1 was started during liver resection and discontinued on POD 3. Postoperative liver function is shown in Fig. 2. Peak levels of AST and ALT were 166 IU/liter and 146 IU/liter, respectively, on POD 1. Serum T. Bil. values were 2.1 mg/100 ml on POD 1. Postoperative course was uneventful, and the patient was discharged from hospital on POD 25.

**Case 3**

The patient was a 62-year-old man with HCC on a cirrhotic liver despite negative serological viral markers. The 10 cm diameter tumor was located in the right lobe and indicated ICG R\textsubscript{15} of 15.0% and a k value of 0.112. An o-GTT test showed a DM pattern. Because liver function was impaired, the patient underwent preoperative right portal vein embolization to reduce postoperative risk after hepatectomy (Makuuchi et al. 1990). Abdominal CT scan preceding hepatectomy showed 11% enlargement of the left lobe as estimated by CT volumetry. Elevation was shown in ICG R\textsubscript{15} to 19.0% and the k value to 0.103. Four weeks
Fig. 3. Postoperative course in Case 3.

Fig. 4. Postoperative course in Case 4.
proceeding embolization, right hemihepatectomy was performed by the controlled method through celio-thoracotomy. Intraoperative blood loss was 2100 ml and operating time was 6 hours. Continuous infusion of PGE$_1$ was started during liver resection from a heparin-coated catheter inserted into the SMA prior to the operation. The infusion rate was 0.01 $\mu$g/kg/min. It was discontinued on POD 5.

Postoperative course in Case 3 is depicted in Fig. 3. Peak values of AST and ALT were 185 IU/liter and 139 IU/liter, respectively, on POD 1. Serum T.Bil. was also highest on POD 1 with a value of 3.7 mg/100 ml. Bile flow from the external biliary drainage tube was 200 ml to 300 ml during PGE$_1$ infusion and it did not change after the cessation of PGE$_1$ via the SMA. Ascites was present during PGE$_1$ infusion via the SMA. On POD 5, portal blood flow was measured by color Doppler US after PGE$_1$ infusion had been stopped for a couple of hours. One hour after restarting PGE$_1$ infusion, portal blood flow was measured again and the flow rate was increased from 450 ml/min to 840 ml/min accompanying PGE$_1$ infusion via the SMA. The patient was doing well and was discharged on POD 22.

Case 4

The patient was a 59-year-old man who presented a huge mass on his right upper abdomen. Abdominal CT scan revealed a large tumor in the liver right lobe and the medial segment preoperatively diagnosed as cholangiocellular carcinoma. Differing from other cases presented herein, liver function was within normal range in this patient: ICG R$_{15}$ was 6.8% and the k value was 0.168. Right trisegmentectomy was performed through a celio-thoracotomy. Intraoperative blood loss was 3050 ml and operating time was 12 hours. The resected specimen weighed 1720 g. Continuous infusion of PGE$_1$ from a catheter inserted in the SMA was started during liver resection at a rate of 0.01 $\mu$g/kg/min and was discontinued on POD 6.

Postoperative liver function in Case 4 is shown in Fig. 4. Peak values of AST and ALT were 377 IU/liter and 460 IU/liter, respectively, on POD 1. Serum T.Bil. was also highest on POD 1 with a value of 1.7 mg/100 ml. Ascites was also present in this case while PGE$_1$ was infused via the SMA. On POD 5, portal blood flow was measured by color Doppler US. One hour after restarting PGE$_1$ infusion, portal blood flow was measured again, and the flow rate had increased from 340 ml/min to 480 ml/min accompanying PGE$_1$ infusion. The patient required thoracocentesis several times to remove pleural effusion, but he was discharged on POD 47.

**DISCUSSION**

We have recently reported efficacy of HA infusion of PGE$_1$ for acute liver failure after hepatic resection (Sato et al. 2000a). Expecting similar beneficial results, we applied intraarterial PGE$_1$ infusion to reduce liver injury and increase safety after major hepatic resection in some high-risk cases presented in the study. As for these four subject, three were accompanied by liver cirrhosis or chronic hepatitis. From ICG test results, these cases should be excluded from right hemihepatectomy according to Makuuchi's criteria (Makuuchi et al. 1993). In addition, they all had DM, which has been reported to increase postoperative morbidity (Shimada et al. 1994). In Case 2, heart dysfunction was also present.

There have been many reports on the PGE$_1$ infusion efficacy against liver damage. Among various mechanisms, the principal action is a vasodilatory effect on vascular smooth muscles (Weiner and Kaley 1969) which results in increased liver blood flow. Anti-platelet action (Himmelreich et al. 1993) or anti-leukocyte adherence action (Natori et al. 1997) might be essential for improved organ microcirculation. In addition, direct PGE$_1$ cytoprotective action
may be involved (Mizoguchi et al. 1987).

Two main aims in administering PGE₁ directly to the liver as opposed to systemic intravenous infusion were: drug delivery advantages and the direct effect on hepatic hemodynamics. With respect to efficacy of drug delivery, both Totsuka et al. (1995) and Kawachi et al. (1997) proved the superiority of intraportal infusion over iv infusion. Since HA infusion is as efficient as portal venous infusion with respect to drug delivery, HA infusion should be more advantageous than iv infusion.

With respect to hepatic hemodynamics, the authors have recently reported that HA infusion of PGE₁ significantly increased HA flow and total hepatic blood flow compared with iv infusion in swine (Sato et al. 2000a). Nakai et al. (1998) also reported increased HA flow caused by HA infusion of PGE₁, while such increase was not observed when administered intraportally. In addition, increased HA flow resulted in increased oxygen supplied to the liver in our animal experiments (Sato et al. 2000a). Oxygen delivery to the liver must be crucial in reducing liver damage after liver resection because sufficient oxygen is indispensable for active metabolism and cell proliferation during liver regeneration.

Insofar as controlled trials are not done, it is quite difficult to prove that HA PGE₁ infusion was singularly responsible for beneficial outcomes. However, in Case 1, the peak value of serum T.Bil. was low even though THVE was executed. It is known that THVE affects liver function much more strongly than liver inflow occlusion (Sato et al. 1998). The authors have also proven HA infusion of PGE₁ efficacy for liver damage after THVE in animal experiments (Sato et al. 2000c). In Case 1, bile flow decreased when PGE₁ infusion was stopped. This observation concurs with the authors’ report (Sato et al. 2000a, c); bile flow increased significantly as a result of arterial infusion of PGE₁ in experiments and in clinical cases.

To obtain more detailed portography by increased SMA blood flow (Clark et al. 1980), PGE₁ infusion via the SMA has been applied. In animal experiments in a pig model of hepatic artery occlusion, continuous infusion of PGE₁ to the SMA markedly increased portal blood flow (Sato et al. 2000b). The increase demonstrated an improvement of 35% over pre-infusion flow at 30 minutes at a rate of 0.02 μg/kg/min; the value was significantly higher than iv infusion. Increased flow resulted in a significant increase in oxygen delivery to the liver. Consistent with this observation, marked increases in portal blood flow were observed in Case 3 and Case 4. Moreover, increases persisted for 5 to 6 days. On the other hand, with respect to drug delivery of PGE₁ to the liver, approximately 45% of PGE₁ reaches the liver after passing the intestines (Awad et al. 1996). Therefore, it should be more efficient to infuse PGE₁ to the SMA than to infuse it intravenously.

Considering side effects of intra-arterial infusion of PGE₁, there was no side effect observed in HA infusion. Since the inactivation rate of PGE₁ in the liver reaches 70% to 90% (Ferreira and Vane 1967), PGE₁ concentration, which flows out of the liver and lung before reaching systemic circulation, should be very low. On the other hand, in both cases of SMA infusion, ascites was generated during PGE₁ infusion. This might owe to increased portal blood flow, but it did not cause body fluid and electrolyte imbalance in these cases. In Case 3 and Case 4, when the infusion rate was increased to 0.02 μg/kg/min transiently, both patients complained of abdominal pain, probably caused by a strong peristalsis. Therefore, the dosage should not reach 0.02 μg/kg/min in cases of SMA infusion.

This report describes two methods, infusion of PGE₁ from either the HA or the SMA, to improve liver function after major hepatic resection. Creation of an access route to the HA or
the SMA can be constructed safely without adding considerable risk to the patient. However, it is still unclear which procedure is preferable to treat such patients. From the authors’ clinical experience and animal experiment results, the present strategy can be outlined as follows. In case the HA is patent and/or the hepatectomy is not major; i.e., less than segmentectomy, in a severely diseased liver, HA infusion might be the superior choice because it provides for full ability of cytoprotective actions and bile excretion function by PGE₁. When hepatic arterial supply is disturbed or insufficient in some parts of the residual liver, there is no alternative aside from SMA infusion. In case portal blood flow would play an important role after major hepatic resection such as in Case 4, SMA infusion might be the better choice because portal blood is known to contain invaluable substances for liver regeneration (Starzl et al. 1978).

CONCLUSION

Although further studies including controlled trials are necessary to prove effectiveness of this treatment, findings in this report suggest that intra-arterial infusion of PGE₁ can reduce liver damage after liver resection. Thus, intra-arterial infusion of PGE₁ has the potential to expand indication of liver resection for patients with poor hepatic functional reserve.

References


