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Is Prostaglandin E_1 (PGE_1) Administration during Hepatectomy Useful in Protecting Hepatic Functions?

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Abstract

During hepatectomy, prostaglandin E_1 (PGE_1) was continuously administered to examine its usefulness in protecting hepatic functions.

Study 1 : 86 patients undergoing hepatectomy were divided into two groups: Group 1 (control group without PGE_1 treatment) and Group 2 (continuous treatment with 20-50ng/kg/min PGE_1 given intravenously during surgery).

GOT, GPT rose rapidly after surgery in both group. Seven days after surgery were required for these parameters to return to their preoperative levels. After surgery, total bilirubin rose over time in both groups, reaching a peak on day 7. After surgery, in terms of the values of serum transaminases and bilirubin, no significant differences between groups were observed. Out of the 86 patients, 29 patients in whom only one hepatic segment or a part of one segment was resected, we re-evaluated similar recovery course of liver functions. In both groups, GPT and GOT rose during the first two days after surgery, but decreased thereafter (a more rapid decrease occurred in Group 2). After surgery, total bilirubin rose in both groups, although the degree of increase was smaller in Group 2.

Study 2: Resected liver tissues were examined for PGE_1 concentrations, energy charge and lactate/pyruvate ratio. This results revealed a significant positive correlation between the total dose of PGE_1 used in this study and the hepatic energy charge ($P < 0.0001$), and a significant negative correlation between the total dose of PGE_1 used in this study and the lactate/pyruvate ratio in liver tissue ($p < 0.05$).

These results indicate that PGE_1 treatment during hepatectomy should be helpful in protecting liver cells and in improving postoperative hepatic fuctions.

Key word : Prostandin E_1, Hepatictomg, Hepatifunction

Introduction

Prostaglandin E_1 (PGE_1) is known to dilate peripheral blood vessels[1) 2) 3)], to suppress platelet aggregation[4) 5)] and to protect functions of the liver and kidney[6) 7) 8) 9)]. It is widely used clinically and its evaluations has been demonstrated in many studies[10) 11) 12]. Hepatectomy has a large unfavorable influence on postoperative hepatic functions. In results, liver function is frequently reduced by anesthesia or surgery. Factors probably responsible for such a reduction in liver functions include the use of anesthetics[13) 14) 15], surgical manipulations[216)], blood transfusion, intraoperative reduction in hepatic blood flow[17)] and the use of various drugs during surgery. Reduction in liver function due to these factors has been regarded as unavoidable. However, even when liver cell injury caused by the anesthetics themselves is minimal, combined with hypoxia or hypotension the reducing reaction of anesthetics in vivo is promoted, leading to severe liver cell

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injury.

In the present study, we assessed the effect of continuous treatment with very low dose of PGE_1 in protecting the liver functions during hepatectomy.

Subjects and Methods

This study was approved by the First Department of Surgery and the Department of Anesthesiology of Hyogo College of Medicine.

Study 1; Clinical evaluations of PGE_1 treatments in hepatic functions.

Included in Study 1 were 86patients who underwent a hepatectomy at the First Department of Surgery, Hyogo College of Medicine Hospital.

Patients were anesthesized with neurolept anesthesia plus oxygen, nitrous oxide (NLA-method) using fentanyl. When blood pressure elevated unfavorably, low concentration of enflurane (0.2-1.5 %) were used. Patients were divided into two groups at randam; Group 1 (without PGE_1 treatment during surgery) and Group 2 (intravenous PGE_1 administration, 20-50 ng/kg/min during surgery). In both groups, GOT (glutamic oxaloacetic transaminase), GPT (glutamic pyruvate transaminase) and total bilirubin were measured to access hepatic functions before surgery and on day 1 through day 7 after surgery. Out of the 86 patients, 29 patients in whom only one hepatic segment or a part of one segment was resected, we evaluated similar recovery course of the liver functions.

Study 2; Evaluations of PGE_1 for energy metabolism in resected liver tissue.

Thirteen patients undergoing hepatectomy were divided at random into three groups: Group 1 (without PGE_1 treatment), Group 2 (a low-dose PGE_1 treatment, 20 ng/kg/min) and Group 3 (a high-dose PGE_1 treatment, 150-200ng/kg/min). As in study 1, the NLA method was the primary method of anesthesia.

From each resected liver tissue sample, a normal portion as remote as possible from the tumor-affected region was collected for weighing and subsequent freezing in liquid nitrogen (-80℃) using the freeze clamp method. Immediately before examination, the frozen liver tissue was subjected to deproteinization in cooled 6% perchloric acid. The tissue was immediately homogenized after deproteinization. Extracts were centrifuged at 10,000 g and 4℃ for 15minutes. The supernatant was neutralized in 69% K_2CO_3 to a pH of 6, followed by cold ultracentrifugation. The supernatant was provided for measurement of adenosine triphosphate (ATP), adenosine diphosphate (ADP) and adenosine monophosphate (AMP) by HPLC (high performance liquid chromatography)[18)19)], and for measurement of lactate and pyruvate by the enzymatic method. Energy Charge (EC; an index of energy level) was calculated using the equation proposed by Atkinson,[15)]

$$EC = (ATP + 0.5\,ADP)/(ATP + ADP/AMP).$$

The resected liver tissues were also provided for measurement of tissue PGE_1 concentration as follows. The sample was homogenized with petroleum ether and ethyl acetate, and then centrifuged. After evaporation and extraction with a buffer solution, the sample was examined for PGE_1, by radioimmuno assay (RIA). For intragroup comparison, the student's t-test was employed. For intergroup comparison, analysis of variance (ANOVA) was used. $P < 0.05$ was regarded as statisically significant.

Results

Study 1: Clinical evaluation of PGE_1 treatments in hepatic functions.

Of the 86 patients, 79 had primary liver cell carcinoma. No significant inter-group difference was observed in the incidence of complications due to liver cirrhosis, age, the results of preoperative indocyanine green (ICG) elimination test, the amount of blood loss during surgery, and the volume of blood transfused (Table 1). Preoperative GPT was 63.8 ± 48.2 KU in Group 1 and 57.5 ± 34.5 KU in Group 2. In both groups, GPT rose over 200 KU on day 1 after surgery, but returned to the preoperative level on day 7 after surgery. Preoperative GOT was 60.1 ± 38.9 KU in Group 1 and 52.2 ± 26.6 KU in Group 2. In both groups, GOT rose to a value over 200 on day 1 after surgery, but returned

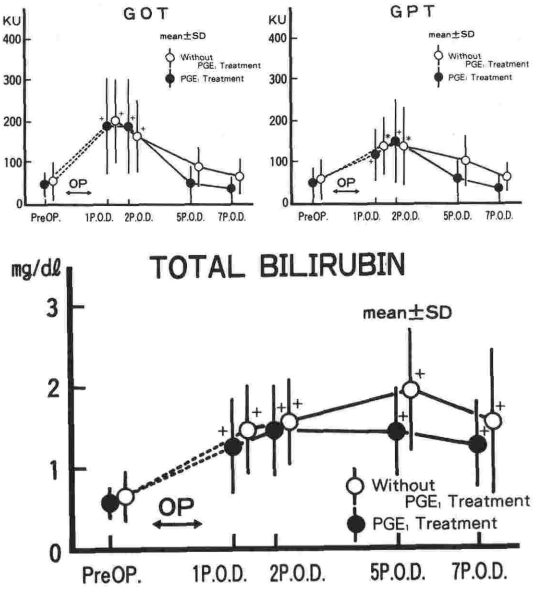
to the preoperative level on day 7 after surgery. Preoperative total bilirubin was 0.63±0.27mg/dℓ in Group 1 and 0.63±0.33mg/dℓ in Group 2. After surgery, total bilirubin rose over time in both groups, reaching a peak on day 7. After surgery, in terms of the values of serum transaminases and bilirubin, no significant differences between groups were observed (Table 2). Out of the 86 patients, 29 patients in whom only one hepatic segment or a part of one segment was resected, we re-evaluated similar recovery course of liver functions (Figuer 1). Preoperative GPT was slightly higher in Group 1 (69.0±43.4 KU; N=15) than in Group 2 (56.0±38.1 KU; N=14). In both groups, GPT rose during the first two days after surgery, but decreased thereafter (a more rapid decrease occurred in Group 2). GPT showed a change similar to that of GOT, with a lower increase and more rapid normalization in Group 2. Preoperative total bilirubin was 0.68±0.33mg/dℓ in Group 1 and 0.58±0.22mg/dℓ in Group 2. After surgery. Total bilirubin rose in both groups, although the degree of increase was smaller in Group 2.

Table 1. Clinical characteristics of 86 patients undergoing hepatectomy. Results are presented as mean±SD.

	Without PGE_1 Treatment	PGE_1 Treatment
Case Number	54	32
Liver Cirrhosis Number	35	20
Age (yr)	58.9±8.8	59.5±8.4
K.ICG	0.128±0.041	0.133±0.043
ICG.R15(%)	17.1±9.1	14.5±8.3
Blood Loss (gram)	1634±959	2254±1261
Transfusion (ml)	1754±1003	1705±1257

Table 2. Changes in GOT, GPT and total bilirubin in PGE_1 treatment group (n=54) and PGE_1 untreatment group (n=32) in the perioperative period. Values are mean±SD. +$p<0.01$ different from pre-operative value for two groups by paired t-test. There no significant differences between two groups by ANOVA.

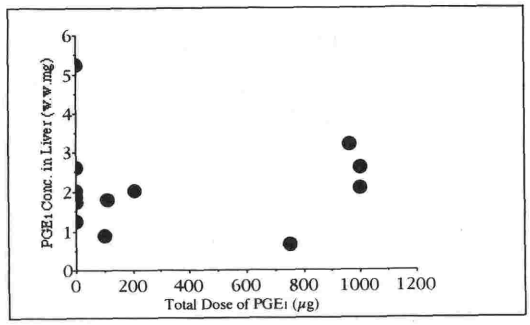
		Pre. OP.	End OP.	1P.O.D.	2P.O.D.	5P.O.D.	7P.O.D.
GOT	PGE_1+	52.2±26.5	125.2±75.7 +	227.0±175.6 +	217.1±185.4 +	80.3±90.6	52.7±42.4
	PGE_1−	60.1±38.9	138.3±68.2 +	203.4±178.9 +	190.0±229.7 +	69.7±34.1	56.5±26.6
GPT	PGE_1+	57.5±34.5	72.7±41.3	148.5±140.6 +	154.9±119.2 +	94.9±96.2	60.3±68.7
	PGE_1−	63.8±48.2	96.2±59.2 +	139.2±127.9 +	166.8±224.6 +	79.1±66.2	51.7±33.8
Total Bilirubin	PGE_1+	0.66±0.33	1.30±0.65 +	1.60±0.89 +	1.75±0.79 +	1.80±0.83 +	1.42±0.71 +
	PGE_1−	0.63±0.27	1.26±0.82 +	1.48±0.71 +	1.62±0.70 +	1.77±0.87 +	1.46±0.95 +



Figuer 1. Changes in GOT, GPT, and total bilirubin in each group undergoing one liver segment or a part of liver segment hepatectomy (solid circle, with PGE_1 treatment group; open circle, without PGE_1 treatment group). Values are mean ± SD. $*p<0.01$ and $+p<0.05$ differrent from preoperative value for two groups by paired t-test. There were no significant differences between two groups by ANOVA.

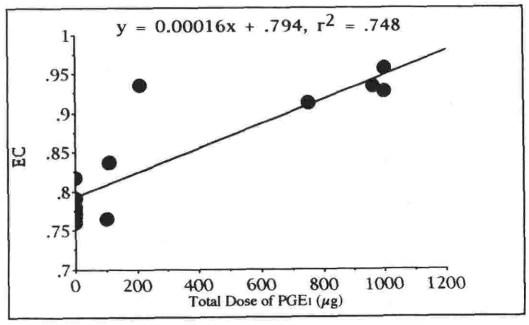
Study 2: Evaluations of PGE_1 for energy metabolism in resected liver tissue (Table 3).

Liver tissue PGE_1 concentration did not differ among the group 1, 2 and 3. ATP and ADP showed no significant inter-group difference, while AMP was significantly lower in the high-dose PGE_1 treatment group than in the other two groups. Energy charge was significantly higher in the high-dose PGE_1 treatment group than in the other two groups. The liver tissue lactate/pyruvate ratio was lower in the high-dose PGE_1 treatment group. There were no statistically significant. No significant correlation was noted between the total PGE_1 dose used and the concentration of PGE_1 in the resected liver tissue ($r^2=0.0003$, $p=0.953$) (Figuer 2). However, the total dose of PGE_1 used during surgery had a significant correlation with the energy charge ($r^2=0.748$, $p<0.0001$) and the lactate/pyruvate ratio ($r^2=0.539$, $P<0.05$) (Figuer 3).

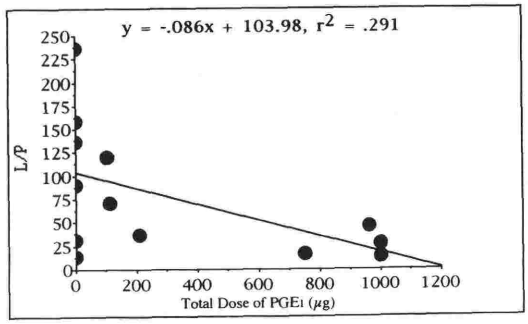


Figuer 2. Relationships between total PGE_1 dose used during surgery and PGE_1 concentration in resected liver tissue ($n=13$, $\gamma^2=0.0003$, $P=0.953$)

(A)



(B)



Figuer 3. (A) Relationships between total PGE_1 dose used during surgery and energy charge ($n=13$, $r^2=0.748$, $p<0.0001$).

(B) Relationships between total PGE_1 dose used during surgery and lactate/pyruvate (L/P) ($n=13$, $r^2=0.291$, $p<0.05$)

Table 3. Concentrations of ATPP, ADP, AMP, lactate, pyruvate and PGE_1 in resected liver tissue in 14 patients.

	Without PGE_1 Treatment n=6	A Low-Dose PGE_1 Treatment n=3	A High-Dose PGE_1 Treatment n=4
PGE_1 Concentration in Liver (pg/w.w.mg)	2.458±1.312	1.578±0.499	2.153±0.943
ATP (μmol/w.w.g)	0.337±0.028	0.328±0.034	0.304±0.029
ADP (μmol/w.w.g)	0.359±0.209	0.497±0.043	0.235±0.076
AMP (μmol/w.w.g)	0.535±0.356	0.800±0.166	0.111±0.040
Energy Charge	0.466±0.132	0.361±0.049	0.922±0.451
Lactate (mg/w.w.g)	1.313±0.383	1.533±0.217	1.527±0.156
Pyruvate (mg/w.w.g)	0.036±0.051	0.023±0.012	0.077±0.039
L/P	102.3±73.7	93.5±52.0	25.8±13.0

Discusssion

PGE_1 is used in various clinical fields, including clinical anesthetic management, ICU and outpatient pain management[21)22)]. Because it is a potent vasodilator, it is frequently used to induce artificial hypotension, to control abnormal elevation in blood pressure during surgery, and to treat ischemic heart diseases, acute circulatory failure and pulmonary hypertension. It is also used to suppress platelet aggregation and to preserve the function of the liver and kidneys[6)7)8)9)]. Like this, the clinical usefulness of this drug has been reported by many investigators.

Patients who undergo hepatectomy often have a liver condition close to cirrhotic liver and are likely to develop massive bleeding and hypotension due to hepatectomy, non-uniform blood flow distribution though organs due to anesthetics, and hypoxia due to disturbed lung ventilation. In such patients, it is essential to prevent hypoxia, to maintain hepatic blood flow and to reduce hepatic dysfunctions. A major goal in the anesthetic management in patients undergoing hepatectomy is to deal promptly with massive bleeding during surgery and prevent a reduction in liver functions as far as possible. PGE_1 may suppress liver injury by the following mechanisms: (1) stabilization of the liver cell membrane[23)24)], (2) cytoprotection[24)25)26)]- improvement in energy charge metabolism-, (3) reduction in bile retention through its action to dilate the cholangiole, (4) increase in hepatic blood flow through its vasodilator action, (5) suppression of free radical reproduction[28)], (6) suppression of micro-thrombus formation within the tissue[28)], or (7) an anti-inflammatory action.[29)301)31)]

Slightly anaerobic metabolism of inhalational anesthetics can be induced by enzymes that yield free radicals, which injure liver cells and cause postoperative liver impairment. Postoperative liver impairment is severe in the presence of hypoxia because this condition further promotes enzymatic induction and anaerobic metabolism of volatile anesthetics. In the present study, treatment with PGE_1 elevated the intracellular energy charge and reduced the L/P ratio in a dose-dependent manner. Thus, a cytoprotective effect of PGE_1 in the liver was suggested by this study. In a dog model of liver

perfusion after ischemia, liver cell ATP was preserved by pretreatment with PGE_1. In an experiment involiving hepatectomy in rats with impaired liver functions, continuous PGE_1 treatment during surgery elevated ATP and cyclic AMP and suppressed the elevation of transaminases, without inducing an increase in liver tissue blood flow. These experimental findings suggest a cytoprotective action of PGE_1 independent of hepatic blood flow.

Rodrigo, et al.[32] recently reported that liver function in patients with fulminant hepatitis was improved rapidly by treatment with PGE_1 (0.2-0.6 micro-gram/kg/hr) for 1-28 days. Utsunomiya[33], et al. reported the effectiveness of 40 micro-gram/day PGE_1 treatment in cases with post-transfusion hepatitis. These two clinical reports endoresd the protective action of PGE_1 on the liver cells. When PGE_1 is used to control blood pressure during surgery, blood flow through vital organs is not reduced simultaneously with a reduction in blood pressure. Because of this feature, PGE_1 has been haighlighted as a safe drug and useful in the control of blood pressure during surgery. Prostaglandin E series have been highlighted because of their cytoprotective action (especially in the pancreas, liver and kidneys).

In the present study, it was not clarified whether the cytoprotective effect of PGE_1 represents a direct action on cells or an indirect action mediated by hepatic blood flow. However, it is well-known that PGE_1 improves hepatic microcirculation and energy metabolism and elevates the arterial blood ketone body ratio-an index of the redox state and energy charge of liver mitochondria-. Furthermore, PGE_1 is known to suppress reductions in liver functions, to increase hepatic and renal blood flow, inducing water and natrium diuresis, and to enhance the production and supplementation of clotting factors. These previous findings and the findings from the present study indicate that PGE_1 treatment during hepatectomy is effective both theoretically and practically.

Although we examined the PGE_1 level in resected liver tissue, PG is not usually pooled in tissue. Administered PGE_1 is rapidly metabolized by liver 15 hydroxy PG dehydrogenase and the liver PGE_1 level represents the PGE_1 producing capacity of the liver. In view of this, the lack of a positive correlation between the tissue PGE_1 concentration and the total PGE_1 dose or energy charge in the present study is acceptable.

Statistically, there were no results to show the beneficial use of PGE_1 in this study. However, these results indicate that PGE_1 treatment during hepatectomy helps in protecting liver cells and in improving postoperative hepatic fuctions.

We conclude that continious administration of PGE_1 intravenously during hepatectomy should be useful, but the optimum dosage of PGE_1 administered during hepatectomy is still undermined.

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