J Anesth (1994) 8:167–171

Journal of
Anesthesia

Effect of prostaglandin E_1 on arterial ketone body ratio in hepatectomy

J. HAYAKAWA[1], G. YOSHIDA[1], and Y. USUDA[2]

[1] Department of Anesthesia, Kanagawa Cancer Center Hospital, 54-2 Nakao-cho, Asahi-ku, Yokohama, Japan
[2] Department of Anesthesiology, Yokohama City University School of Medicine, Yokohama, Japan

Abstract: We evaluated the effect of prostaglandin E_1 (PGE_1) administration during hepatectomy on arterial ketone body ratio (AKBR), which is an indicator of liver function, and on other liver functions in the postoperative period. Eighteen patients were divided into two groups: Continuous intravenous administration of PGE_1 (0.02 $\mu g \cdot kg^{-1} \cdot h^{-1}$) was started immediately before hepatic resection and ceased at the end of operation in nine patients (PGE_1 group); the other nine did not receive PGE_1 (control group). After hepatic resection, a significant increase in AKBR was observed in the PGE_1 group. However, no change was observed in the control group. In the PGE_1 group, total bilirubin and SGOT recovered more rapidly to the preoperative level than in the control group. These findings suggested that PGE_1 might have a protective effect on the liver.

Key words: prostaglandin E_1, arterial ketone body ratio, postoperative liver function

Introduction

Surgical trauma, which affects the liver directly during hepatectomy, seriously impairs liver function and may occasionally cause fatal postoperative hepatic dysfunction. Therefore, minimizing hepatic damage is required in anesthetic management during hepatectomy. It has been suggested that prostaglandin E_1 (PGE_1) administration during operation may protect the liver function [1–3]. Hence, we administered PGE_1 in patients who underwent hepatectomy and observed changes in the arterial ketone body ratio (AKBR) as an index of the redox state of mitochondria in hepatocytes. In addition, we evaluated the effect of PGE_1 administered during operation on the postoperative liver function.

Address correspondence to: J. Hayakawa
Received for publication on December 25, 1992; accepted on November 9, 1993

Subjects and methods

The subjects were 18 patients who underwent hepatectomy because of hepatocellular carcinoma. They gave their informed consent to participate in this study before operation. They were divided into two groups, one of which received PGE_1 during operation in 9 cases (PGE_1 group), and the other of which did not receive PGE_1 in 9 cases (control group).

Thirty minutes before induction of anesthesia, atropine 0.5 mg and diazepam 10 mg were intramuscularly injected as premedication and 5 $mg \cdot kg^{-1}$ thiopental and 0.1 $mg \cdot kg^{-1}$ pancuronium were administered intravenously for the induction of anesthesia followed by endotracheal intubation. The anesthesia was maintained thereafter by inhalation of oxygen and nitrous oxide and intravenous drip infusion of ketamine (0.5–2.0 $mg \cdot kg^{-1} \cdot h^{-1}$) plus occasional administration of diazepam. Controlled ventilation was obtained by the intermittent administration of pancuronium. Hartman solution containing glucose was administered at 5 $mg \cdot kg^{-1} \cdot h^{-1}$ in combination with 4–5 $mg \cdot kg^{-1} \cdot h^{-1}$ of fresh frozen plasma throughout the operation. A cannula was inserted in the radial artery for continuous measurement of the arterial pressure and collection of blood sample for chemical analysis.

The measurements of blood pressure and heart rate, arterial blood gas analysis, blood sugar, and blood collection for examinations of AKBR, were performed at the beginning of operation, immediately before hepatic resection (preresection), immediately after hepatic resection (postresection), and at the end of operation. In the PGE_1 group, after pre-resectional measurement and blood collection, 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ PGE_1 was continuously administered until the end of operation. In both groups, serum total bilirubin (T-bil), SGOT, and SGPT were evaluated before operation, immediately after operation, and at 1, 3, 7, 14, and 21 days after operation.

Patients in whom hepatic blood flow was occluded temporarily during hepatic resection were excluded from the analysis of data.

Ketone bodies were measured by the colorimetric method [4,5] blood sugar and T-bil were measured by the enzyme method, SGOT and SGPT were measured by initial rate assay, and arterial blood gases and pH were measured by a pH/blood gas analyzer (Corning, Ithaca, N.Y.). The above results were statistically analyzed by the paired *t*-test or analysis of variance. Differences were considered significant when $P < 0.05$.

Results

There were no significant differences in the patients' backgrounds between the PGE_1 and the control groups, as shown in Table 1.

Mean blood pressure and heart rate (Table 2)

No significant changes between the stages and groups were noted in mean blood pressure.

Heart rate remained essentially unchanged throughout but decreased slightly in the control group immediately before the resection. None of the cases remained below 80 mmHg of systolic blood pressure more than momentarily.

Pao2 (Table 2)

Although Pao_2 was significantly higher postresection than at the end of operation in the control group, no other significant change was observed between either the stages or groups. No hypoxemia ($Pao_2 <$ 100 mmHg) was noted during the operation.

AKBR (Fig. 1)

In the control group, AKBR decreased gradually after commencement of the operation, and recovered at the end of operation. Conversely, in the PGE_1 group, AKBR decreased similarly until the preresection stage and then increased up to the initial level. AKBR was significantly higher in the PGE_1 group at the postresection stage than that in the control group.

Acetoacetate and β-hydroxybutyrate (Table 3)

Both acetoacetate and β-hydroxybutyrate showed no significant change between either the stages or groups.

Table 1. Patient characteristics (mean ± SD)

	Control group	PGE_1 group
No. of patients (M/F)	9 (7/2)	9 (7/2)
Age (years)	60.1 ± 7.2	63.6 ± 6.9
Weight (kg)	57.9 ± 9.5	60.8 ± 10.9
Duration of operation (min)	297 ± 144	315 ± 142
Blood loss (g)	1994 ± 1220	2361 ± 1082
Urine volume (ml)	623 ± 602	821 ± 504
Blood transfusion (ml)	1600 ± 974	1888 ± 927
Liver cirrhosis (with/without)	5/4	6/3
No. of resected subsegments[a] (1/2/3)	3/5/1	6/2/1

There are no significant differences between the two groups.
[a] according to Couinoud's classification.

Table 2. Change in mean arterial pressure, heart rate, and Pao_2 during hepatectomy

		I	II	III	IV
Mean arterial pressure	control group	103 ± 12	96 ± 13	102 ± 13	98 ± 16
(mmHg)	PGE_1 group	93 ± 10	100 ± 9	97 ± 9	103 ± 10
Heart rate	control group	80 ± 9	73 ± 6*	80 ± 11	84 ± 10
(bpm)	PGE_1 group	82 ± 8	82 ± 11	84 ± 5	86 ± 8
Pao_2	control group	168 ± 45	157 ± 36	169 ± 37**	150 ± 38
(mmHg)	PGE_1 group	155 ± 43	151 ± 44	173 ± 31	172 ± 33

I, beginning of operation; II, preresection; III, postresection; IV, end of operation. Values are expressed as mean ± SD.
* $P < 0.05$ *vs* III and IV; ** $P < 0.05$ *vs* IV.

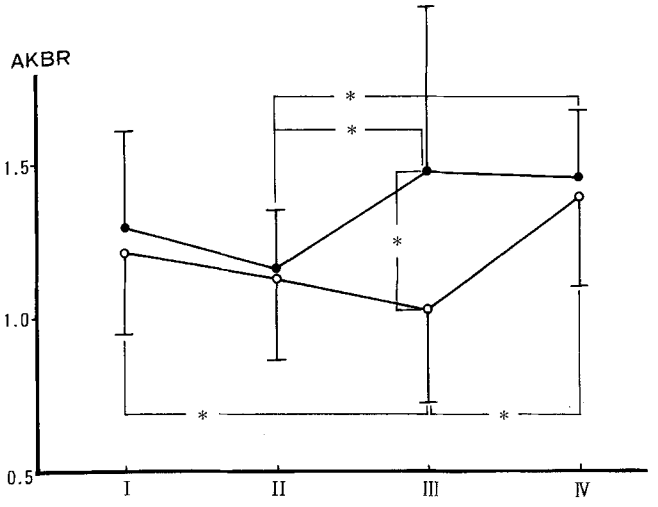

Fig. 1. Change in arterial ketone body ratio (AKBR) during hepatectomy. I, beginnig of operation; II, preresection; III, postresection; IV, end of operation; *open circles*, control group; *closed circles*, PGE_1 group. $*P < 0.05$

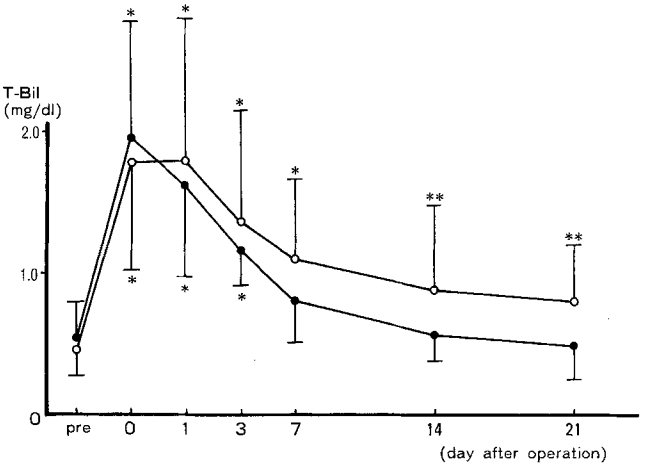

Fig. 2. Change in total bilirubin (T-bil) after hepatectomy. pre, preoperative period; *open circles*, control group; *closed circles*, PGE_1 group. $*P < 0.01$ and $**P < 0.05$ *vs* preoperative period

Blood sugar (Table 3)

Blood sugar remained over 150 $mg \cdot dl^{-1}$ in both groups throughout.

T-bil (Fig. 2)

T-bil increased sharply and reached a peak immediately after the operation and then decreased gradually in both groups. Although it recovered to the initial level at 7 days after operation in the PGE_1 group, it remained at a higher level in the control group than the preoperative level even at 21 days after operation. There was, however, no significant change between the groups in any variable.

SGOT (Fig. 3)

SGOT increased after operation then decreased, with a peak at 1 day after the operation, in both groups. Although in the PGE_1 group it recovered to the preoperative level at 7 days after operation, in the control group it recovered to the preoperative level at 21 days after operation. There was, however, no significant change between the groups in any variable.

SGPT (Fig. 4)

Similar to SGOT, SGPT increased and peaked at 1 day after the operation and then decreased in both groups.

There was no change in recovery to the preoperative level between the groups and there was no significant change between the groups in any variable.

Discussion

AKBR stays in equilibrium with the redox state of mitochondria in the liver and is highly correlated with the level of hepatic energy charge, which plays an important role maintaining the function of liver cells. Therefore, AKBR is a useful index of the change in liver

Table 3. Change in acetoacetate, β-hydoroxybutyrate, and blood sugar during hepatectomy

		I	II	III	IV
Acetoacetate	Control group	25.7 ± 7.1	22.2 ± 4.9	20.9 ± 4.3	26.3 ± 8.8
(μ mol · l^{-1})	PGE_1 group	31.6 ± 11.2	22.9 ± 5.9	23.2 ± 6.1	24.2 ± 5.4
β-hydroxybutyrate	Control group	21.5 ± 10.3	19.7 ± 7.9	20.4 ± 8.1	18.8 ± 5.8
(μ mol · l^{-1})	PGE_1 group	24.4 ± 14.7	20.3 ± 9.2	15.6 ± 4.6	16.9 ± 5.9
Blood sugar	Control group	186 ± 37	222 ± 58	224 ± 68	236 ± 54*
($mg \cdot dl^{-1}$)	PGE_1 group	176 ± 26	198 ± 31	207 ± 38*	202 ± 35*

I, beginning of operation; II, preresection; III, postresection; IV, end of operation. Values are expressed as mean ± SD.
$* P < 0.05$ *vs* I.

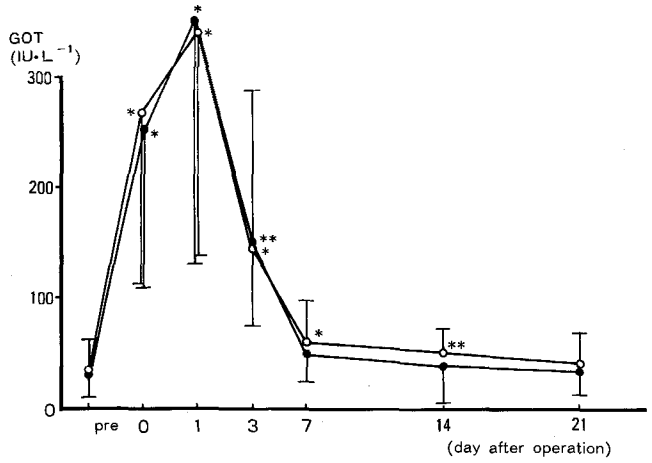

Fig. 3. Change in SGOT after hepatectomy. pre, preoperative period; *open circles*, control group; *closed circles*, PGE_1 group. $*P < 0.01$ and $**P < 0.05$ *vs* preoperative period

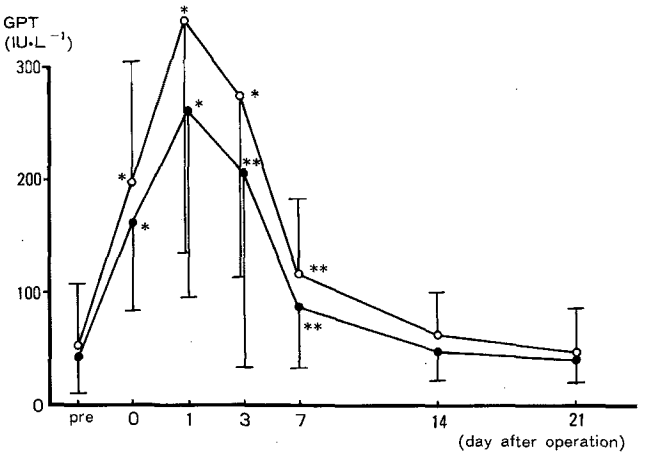

Fig. 4. Change in SGPT after hepatectomy. pre, preoperative period; *open circles*, control group; *closed circles*, PGE_1 group. $*P < 0.01$ and $**P < 0.05$ *vs* preoperative period

function [6–9]. The blood sugar level [10], hypotension due to bleeding [11], and hypoxemia [11] other than surgical procedure are considered to be factors affecting AKBR during operation. When blood sugar decreases with the preoperative fasting, AKBR usually decreases as well [10]. In this study, however, the blood sugar level was maintained higher than 150 $mg \cdot dl^{-1}$, which has been said not to affect AKBR [12], and hence hypoglycemic effect would be excluded as a factor associated with AKBR. Continuous hypotension decreases AKBR by decreasing hepatic blood flow. Also hypoxemia decreases AKBR by decreasing oxygen supply to the liver [10]. In this study, however, there were no cases which had prolonged hypotension or hypoxemia, and hence these might be also excluded from factors affecting AKBR value. Therefore, the change in AKBR in this study could reflect the effect of surgical trauma on the liver and might have been improved by the effect of PGE_1 on the liver.

The results obtained in this study suggest that PGE_1 attenuates the decrease in AKBR which usually occurs due to surgical stress during hepatic resection. These results may show that surgical procedures during hepatectomy directly affect the liver by decreasing hepatic blood flow, and that PGE_1 protects liver function during hepatectomy. It has been reported that PGE_1 cannot prevent the decrease in AKBR during hepatic ischemia but that it can promote an increase in AKBR after reperfusion [13]. In this study, data were obtained only in cases in which the hepatic blood flow was never occluded. Therefore, it is suggested that PGE_1 cannot protect hepatic cells under the condition in which hepatic blood flow is completely blocked but may protect them if some degree of hepatic blood flow remains, and it may represent a protective effect on hepatic cells even though hepatic blood flow is decreased by surgical procedures. Our previous study [3] has documented that AKBR decreased in association with surgical procedures in the upper abdominal cavity, such as gastrectomy, while it increased following PGE_1 infusion. AKBR increased significantly following PGE_1 infusion even after hepatectomy in this study. In the control group, however, AKBR remained low.

In this study, in the PGE_1 group, liver functions recovered more rapidly to the preoperative level than those in the control group, suggesting protective effect of PGE_1 on liver cells and liver function.

The mechanism of the protective effect of PGE_1 on liver cells is assumed to be the result of inhibition of activity or production of chemical mediators damaging liver cells [14–16], stabilization of hepatic cell membranes [17], and stable microcirculation in the liver [18,19]. The fact that PGE_1 maintains hepatic blood flow satisfactorily during upper abdominal surgery has also been reported [20]. Considering the above reports, the protective effect of PGE_1 on liver cells and liver function may consist of a hemodynamic effect and a direct effect on liver cells.

In conclusion, in this study, PGE_1 not only prevented the decrease in AKBR during hepatectomy, but also promoted recovery of postoperative liver function.

References

1. Ikegaki J, Mikawa K, Ikegaki N, et al. (1991) Protective effects of PGE_1 on postoperative liver function after gastric cancer surgery (in Japanese, with English abstract). Masui (Jpn J Anesthesiol) 40:1193–1197
2. Iwatsuki N, Yasuda A, Tokutomi S, et al. (1992) Preventative effect of PGE_1 for postoperative liver damage. J Anesth 6:131–137

3. Hayakawa J, Yoshida G, Usuda Y (1992) Effect of prostaglandin E_1 on arterial ketone body ratio during gastrectomy (in Japanese, with English abstract). Masui (Jpn J Anesthesiol) 41:894–899
4. Mellanby J, Williamson DH (1974) Acetoacetate. In: Bergmeyer HV (ed) Methods of enzymatic analysis. Academic Press, New York, pp 1446–1451
5. Williamson DH, Mellanby J (1974) β-hydroxybutyrate. In: Bergmeyer HV (ed) Methods of enzymatic analysis. Academic, New York, pp 1836–1839
6. Tanaka J, Ozawa K, Tobe T, et al. (1979) Significance of blood ketone body ratio as a hepatic energy status in jaundice rabbit. Gastroenterology 176:691–696
7. Yamamoto M, Tanaka J, Ozawa K, et al. (1980) Significance of acetoacetate/β-hydroxybutyrate ratio in arterial blood as an indicator of the severity of hemorrhagic shock. J Surg Res 28: 124–131
8. Ukikusa M, Ozawa K, Shimabara Y, et al. (1981) Change in blood ketone body ratio—Their significance after major hepatic resection. Arch Surg 116:781–785
9. Ozawa K, Fujimoto T, Nakatani T, et al. (1982) Change in hepatic energy charge, blood ketone body ratio, and indocyanine green clearance in relation to DNA synthesis after hepatectomy. Life Sci 31:647–653
10. Kimura K, Ukikusa M, Ozawa K, et al. (1978) Change in mitochondrial redox state following an oral glucose load. Acta Diab Lat 15:283–286
11. Ukikusa M, Ida T, Ozawa K, et al. (1979) The influence of hypoxia and hemorrhage upon adenylate energy charge and bile flow. Surg Gynecol Obstet 149:346–352
12. Shimahara Y, Kiuchi T, Tokunaga Y, et al. (1988) Redox theory of the liver (in Japanese, with English abstract). ICU to CCU (Jpn J Intens Care Med) 12:953–962
13. Nakagawa I, Nishioka K, Kubota M, et al. (1990) Effect of PGE_1 on arterial blood ketone body ratio in hepatomized patients (in Japanese, with English abstract). Masui to Sosei (Hiroshima J Anesth) 26:53–57
14. Mizoguchi Y, Tsutsui H, Miyajima K, et al. (1987) The protective effects of prostaglandin E_1 in an experimental massive hepatic cell necrosis model. Hepatology 7:1184–1188
15. Kawada N, Mizoguchi Y, Hasegawa I, et al. (1989) Synthesis of interleukin 1 by liver adherent cells of Kupffer cells and its regulation with prostaglandin (in Japanese, with English abstract). Kanzo (Liver) 30:1709–1715
16. Kawada N, Mizoguchi Y, Ichikawa Y, et al. (1990) Production of tumor necrosis factor by liver adherent cells and its regulation with prostaglandins (in Japanese, with English abstract). Kanzo (Liver) 30:130–138
17. Masaki N, Ohta Y, Shirataki H, et al. (1992) Hepatocyte membrane stabilization by prostaglandin E_1 and E_2: favorable effects on rat liver injury. Gastroenterology 102:572–576
18. Guemei A, Bashour FA, Swamy BV, et al. (1973) Prostaglandin E_1: Its effects on the hepatic circulation on dogs. Pharmacology 9:336–347
19. Ishida T (1988) The experimental study of PGE_1 infusion on the liver circulation in dogs (in Japanese, with English abstract). J Jpn Surg Soc 89:898–905
20. Doi R, Inoue K, Yun M, et al. (1988) Effect of prostaglandin E_1 on hepatic circulation (in Japanese, with English abstract). Igaku no Ayumi (J Clin Exp Med) 147:575–576