# Preventative Effect of $PGE_1$ for Postoperative Liver Damage

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The efficacy of a low dose of $PGE_1$-use on the postoperative liver damage was evaluated. $PGE_1$ was infused in with the mean rate of 0.026 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during surgical procedure to 93 patients under GO-enflurane anesthesia (the PG). Serum GOT, GPT and total bilirubin (TBIL) values measured before, at the end of (End) and 3 days (3d) after the operation were compared to those obtained from 43 patients without $PGE_1$ administration (the control).

This dose of $PGE_1$ did not change blood pressure and heart rate, but slightly decreased $Pa_{O_2}$. In patients with preoperative normal values of GOT, GPT and TBIL, increases in GOT, GPT and TBIL observed at End in the PG were significantly lower than those in the control (31.9 vs 72.2 IU, 25.9 vs 61.9 IU, 0.68 vs 0.83 $mg \cdot dl^{-1}$, respectively). GOT, GPT and TBIL at 3d significantly increased in both groups, and these levels were identical between the two groups. In patients with preoperative abnormal values, only GOT at End increased in both groups, while no significant difference between the PG and the control group was noted. GOT at 3d and GPT at End and 3d did not significantly changed in either group. These results suggest that the low dose of $PGE_1$ administered during an operation prevents the development of postoperative liver damage, but does not treat the damaged hepatic cells. (Key words: prostaglandine $E_1$, Postoperative liver damage)

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The recent topic regarding prostagrandine (PG) is that PG effectively prevents or treats several types of liver damages induced by chemical substances or virus in experimental animals[1–6]. Moreover, the recent human trial on fulminant viral hepatitis demonstrated the efficacy of $PGE_1$ for the treatment of hepatic failure[7].

Postoperative minor liver damage after general anesthesia has been reported not to be uncommon[8]. We, therefore, evaluated whether or not prophylactic administration of $PGE_1$ with a small dose during surgical procedure prevent development of the postoperative liver damage.

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**Table 1.** Charactalistics of patients and surgical procedure

| | PG (n=93) | Control (n=43) |
|---|---|---|
| Age (Yr) | 55.2 ± 13.6 | 57.4 ± 11.5 |
| Weight (Kg) | 55.4 ± 8.6 | 55.8 ± 8.4 |
| Gender (M/F) | 36/57 | 24/19 |
| Duration of OP (min) | 195 ± 161 | 227 ± 166 |
| Duration of Anes (min) | 235 ± 166 | 267 ± 171 |
| Blood Transfusion | | |
| number of pt | 15 (16%) | 9 (21%) |
| volume (ml) | 872 ± 308 | 822 ± 466 |

Mean ± SD. No significant differences between the PG and the control group. PG = the PG group, Control = the control group, OP = the operation, Anes = anesthesia, pt = patient.

**Table 2.** List of operated organ

| | PG | Control |
|---|---|---|
| Brest | 6 | 0 |
| Upper GI | 28 | 8 |
| Lower GI | 10 | 8 |
| Liver and Pancreas | 21 | 16 |
| Gynecologic | 16 | 5 |
| Others | 12 | 6 |

There are no significant differences between the PG and the control group. GI = gastrointestinal tract. PG = the PG group, Control = the control group.

## Materials and Methods

*Patients*

Ninety three of ASA physical state 1 or 2 adults patients, who provided informed consent and scheduled for surgical operation under general anesthesia, were subjected for the $PGE_1$ administration (the PG group). Patients with heart disease, sever liver and renal dysfunction were excluded from the study. As the control, 43 patients who underwent surgical operation matching to those of the PG group were retrospectively picked up from the anesthetic records from the recent last 4 months. Age, body weight and sex of the patients, duration of the operation and anesthesia, operated organs, number of patients recieved blood transfusion and volume of transfusion did not significantly differ between the PG and the control group (table 1 and 2). An antibiotic was administered to all patients during or immediately after the operation. Patients treated with chemotherapy for malignant neoplasm before or within 3 days after the operation were excluded from the study.

*Protocol and Measurements*

$PGE_1$ in powder (Ono Pharmaceutical Co.) was dissolved with distilled water each time just before the start of the study. $PGE_1$ was administered continuously at the rate of 0.02–0.03 $\mu g \cdot kg^{-1} \cdot min^{-1}$ from the start to the end of the surgical procedure. Anesthesia was maintained with enflurane (1–3%) plus $N_2O$ (50–66%) with epidural anesthesia (31 patients in the PG group and 23 in the control group) or without epidural anesthesia following the induction with iv thiopental.

Venous blood was sampled for the measurements of serum GOT, GPT and total bilirubin (TBIL) before, at the end of (End) and 3 days after the operation (3d). Systemic blood pressure (BP), heart rate (HR), arterial gases and $Pa_{O_2}/F_{I_{O_2}}$ ratio were measured before the operation in both groups, either 30 min after the start of PG administration in the PG group or 30 min after the start of surgical

**Table 3.** Physical charactalistics

| | | PG | Control |
|---|---|---|---|
| SBP (mmHg) | Pre | 119.7±25.5 | 117.0±20.6 |
| | Dur | 114.3±21.2 | 114.3±20.3 |
| | End | 127.1±24.1 | 122.5±33.1 |
| HR (bpm) | Pre | 86.8±14.9 | 86.2±13.5 |
| | Dur | 86.6±16.1 | 87.7±16.3 |
| | End | 83.7±15.9 | 78.6±15.9 |
| $Pa_{O_2}$ (mmHg) | Pre | 174.4±51.9 | 171.7±60.6 |
| | Dur | 155.3±44.4** | 160.3±50.2 |
| | End | 192.0±89.7 | 210.9±121.7 |
| $\frac{Pa_{O_2}}{FI_{O_2}}$ | Pre | 489.9±119.6 | 462.4±117.1 |
| | Dur | 440.3±117.7** | 434.6±138.2 |
| | End | 460.6±119.7 | 453.4±111.6 |
| $Pa_{CO_2}$ (mmHg) | Pre | 35.1±5.0 | 35.9±4.7 |
| | Dur | 34.5±4.6 | 35.2±4.0 |
| | End | 35.0±4.9 | 35.4±3.8 |
| PH | Pre | 7.444±0.049 | 7.439±0.042 |
| | Dur | 7.444±0.047 | 7.445±0.037 |
| | End | 7.430±0.050 | 7.427±0.046 |

Mean ± SD. **: $P < 0.01$ vs preoperative values (Pre).

PG = the PG group, Control = the control group, SBP = systoric blood pressure, HR = heart rate, Pre = preoperative, Dur = 30 min after the start of PG administration or the operation, End = the end of the anesthesia.

**procedure in the control group, and in both groups at the end of anesthesia. All measured values of GOT, GPT and TBIL were expressed with mean ± SE.**

*Analysis*

**Patients with normal values of GOT (< 30 IU) and GPT (< 28 IU) at the preoperative period and those with abnormal values were separately analyzed. Moreover, for GOT and also GPT values measured consecutively at all three periods, namely before, at End and 3d, the paired statistical analysis was performed, since the continuous observation through one patient was possible for them. Fifty six patients in the PG and 16 patients in the control group were suited to this. TBIL was measured on 86 of 93 patients in the PG group and all 43 patients in the control group. Then an analysis of TBIL was performed only on the patients with normal values preoperatively (< 1.1 mg·dl$^{-1}$), since num-**

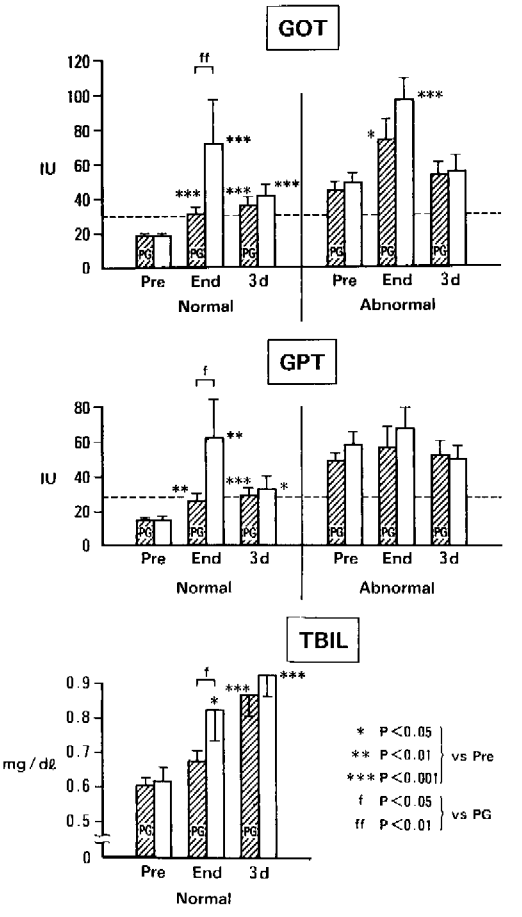


**Fig. 1.** Comparisons of serum GOT, GPT and total bilirubin (TBIL) between the PG group (PG) and the control group (white bars) in all patients studied. Pre = preoperative period, End = the end of the operation, 3d = 3 days after the operation, IU = international unit. "Normal" on abscissa means the group of patients who had a normal value at preoperative period and "Abnormal" is that of an abnormal value. A broken line is the upper limit of a normal value. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, from preoperative values in the same group. f: $P < 0.05$, ff: $P < 0.01$, compared between the PG and the control group at the same period. Values are expressed with mean ± SE.

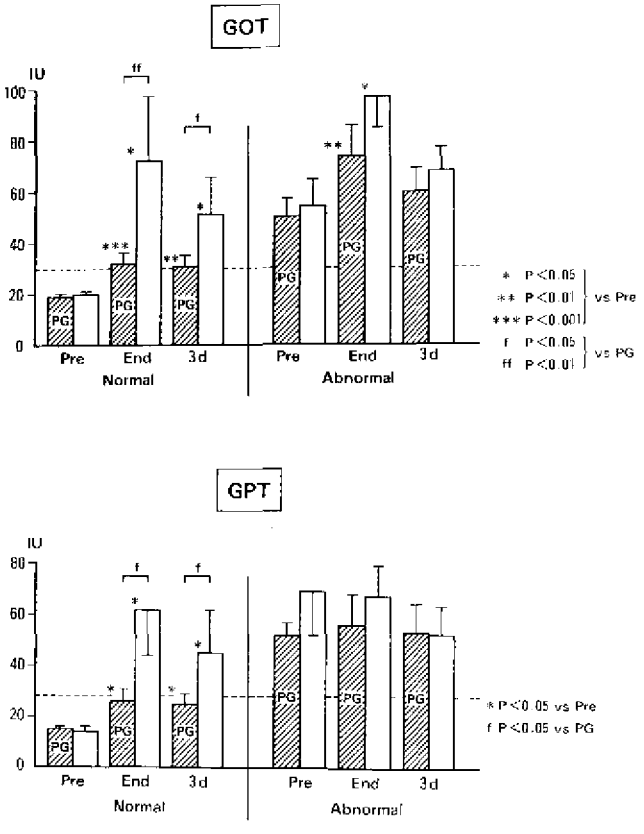


**Fig. 2.** Changes in GOT an GPT in patients who had measurements at all three consecutive periods, namely Pre, End and 3d. PG = the PG group, IU = international unit, Pre = preoperative period, End = the end of the operation, 3d = 3 days after the operation. "Normal" means the group of patients with a preoperative normal value and "Abnormal" is that with an abnormal value. A broken line illustrates the upper limit of a normal value. *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$ from the preoperative values. f: $P < 0.05$, ff: $P < 0.01$, compared between the PG and the control group. Values are expressed with mean ± SE.

ber of patients with abnormal TBIL was too small to statistically evaluate (4 in the PG and 3 in the control).

Student's t test or $X^2$ was used for a statistical analysis of the data. $P$ value less than 0.05 was considered to be significant.

## Results

Mean infusion rate of $PGE_1$ was 0.026 ± 0.013 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (SDM), which did not produced significant decrease in systoric BP (table 3). Absolute values of BP at the comparable three periods did not differ between the PG and the control group (table 3). HR, $Pa_{CO_2}$ and PH were not changed by $PGE_1$ infusion and did not differ between the two groups (table 3). A significant decrease in $Pa_{O_2}$ associated with a decrease in $Pa_{O_2}/FI_{O_2}$ was observed during infusion on $PGE_1$, but did not reach to the hypoxic level.

Seventy six of 93 patients in the PG group and 32 of 43 patients in the control group had normal GOT preoperatively (19.1 ± 0.5, 19.5 ± 0.8 $IU \cdot l^{-1}$, respectively). In normal GOT patients, GOT increased significantly at both periods after the operation in both groups (fig. 1). GOT at End was, however, significantly lower in the PG group (31.9 ± 3.4) than that in the control group (72.2 ± 24.5) (fig. 1). GOT in patients with preoperative abnormal values (44.3 ± 4.9: the PG, 49.0 ± 5.1: the control) also significantly increased at End in both groups (73.2 ± 12.1: the PG, 96.0 ± 11.9: the control), but did not increase at 3d in both groups (52.8 ± 7.2: the PG, 55.4 ± 8.8: the control). There were no significant differences in GOT between the two groups with preoperative abnormal value at both

End and 3d (fig. 1).

GPT was preoperatively normal in 66 of 93 patients of the PG group ($14.9 \pm 0.7$ IU·$l^{-1}$) and 28 of 43 patients of the control group ($15.1 \pm 0.8$). In these patients with normal values GPT significantly increased to $25.9 \pm 4.1$ at End and to $29.3 \pm 4.1$ at 3d in the PG group, and also to $61.9 \pm 22.7$ and $33.3 \pm 7.2$ in the control group, respectively. A significant difference between the two groups was noted at End (fig. 1). Abnormal values of GPT before the operation were $49.4 \pm 3.8$ in the PG group and $57.7 \pm 7.1$ in the control group. These values remained unchanged in the subsequent period ($55.7 \pm 12.3$, $67.8 \pm 11.8$ at End and $51.6 \pm 7.9$, $50.2 \pm 6.5$ at 3d, respectively). There were no significant differences between the two groups at the three periods (fig. 1).

TBIL of the patients with normal values preoperatively in the PG group ($0.61 \pm 0.02$ mg·$dl^{-1}$, n=82) did not change at End ($0.68 \pm 0.03$), but increased significantly at 3d ($0.87 \pm 0.06$). In contrast, those in the control group ($0.62 \pm 0.04$, n=40) significantly increased to $0.83 \pm 0.09$ and $0.93 \pm 0.06$ at End and 3d, respectively (fig. 1). TBIL at End in the PG group was significantly lower than that in the control group (fig. 1).

When the paired statistical analysis was performed for GOT and GPT values measured consecutively at all three periods, namely before, at End and 3d, the difference between the PG and the control group with preoperative normal values of GOT and GPT became more significant, especially at 3d (fig. 2).

Numbers of patients whose GOT became abnormal were 17/45 in the PG and 9/12 in the control group at End ($P < 0.03$), and 15/45 in the PG and 8/12 in the control at 3d ($P < 0.04$). GPT changed to abnormal in 11 of 37 patients in the PG and 6 of 10 in the control group at End ($P < 0.08$), and in 10 of 37 in the PG and 6 of 10 in the control at 3d ($P < 0.06$). $P$ values in a parenthesis mean comparisons between the two groups. Less numbers of patients, therefore, had abnormal GOT or GPT by administration of $PGE_1$.

## Discussion

The present study demonstrated that the administration of $PGE_1$ during surgical procedure with a low dose, which did not decrease systemic blood pressure, prevented the postoperative increase in serum GOT, GPT and total bilirubin (TBIL), and made smaller the number of the patient whose GOT and GPT became abnormal postoperatively. These results suggest a preventative effect of $PGE_1$ for the development of the postoperative liver damage. $PGE_1$, however, may not posses a therapeutic effect to improve the already impaired function of the liver, since preoperative abnormal GOT and GPT were not improved by the administration of $PGE_1$.

Efficacies of PGE to prevent acutely induced liver damages have been reported in the experimental animal models[1–4,6]. In human, fulminant viral hepatitis was effectively treated by $PGE_1$ administration[7]. A cytoprotective effect of $PGE_1$ through an inhibition of activity or production of chemical mediators known to produce cell necrosis or to be toxic for liver cells has been mentioned as one of the possible contributing factors[9–11]; such as interleukin, tumor necrosis factor and platelet activating factor. Stabilization of cell membrane[12] and maintenance of good microcirculation[13,14] to maintain hepatic oxygenation may also be other contributing mechanism for the protective effect of $PGE_1$.

Many causes of postoperative liver dysfunction have been speculated, including hepatic $O_2$ deprivation, acute viral hepatitis, aggravated chronic hep-

atitis, blood transfusion and specific drug therapy[8]. Inhalation of halogenated anesthetics is one of the other causes. The current view has shown two entities for this anesthetic-related hepatic dysfunction[15]. One is rare, delayed in onset, severe and often lethal toxicity, and an immune mediated mechanism might be contributed. The other is seen shortly after anesthesia with a mild degree of damage and rather common. The later form may be the one observed in this study. Although mechanisms of this toxicity have not been defined, many risk factors have been mentioned[8,16]; such as obesity, middle aged, female and hypoxic or ischemic insult to liver. Body weight, age and gender did not differ between the PG and the control group. $Pa_{O_2}$, $Pa_{O_2}/FI_{O_2}$ and blood pressure did not show any differences to produce hypoxic or ischemic episodes between the two groups, and duration of surgical stress was identical in both groups. The chances in suffering from viral hepatitis might be similar between the PG and the control group in this study. Numbers of patients who had blood transfusion during the operation and had a specific drug therapy during perioperative period, such as antibiotics, did not differ between the two groups. Therefore, the lower incidence of increase in GOT, GPT and TBIL observed in the PG group might not be attributed by the differences of the risk factors, but by the administration of $PGE_1$. Of course there is no way to prove from this study, the protective mechanisms of $PGE_1$ suggested in acute experimental liver damages, namely cytoprotective effects, membrane stabilization and effect on hepatic microcirculation, may also play an important role preventing the development of postoperative liver damage.

In conclusion, the low dose of $PGE_1$ infused during surgical procedure effectively prevents the induction of the postoperative liver damage, while it does not improve the liver damage already presented.

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