原 著

Effect of Prostaglandin E_1 on Plasma Lidocaine Concentrations during Epidural Block

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Abstract

We evaluated the effect of prostaglandin E_1 (PGE_1) infusion on plasma concentrations of lidocaine injected into the epidural space during lower abdominal surgery. Fourteen female patients undergoing gynecologic surgery under epidural blockade plus general anesthesia were divided into two groups. In the PGE_1 group (n=7), 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ of PGE_1 was administered intravenously during surgery. In the control group (n=7), patients were not given PGE_1. Plain 1.5 % lidocaine solution was injected through the epidural catheter by 10 ml bolus, followed by continuous administration of 8 $ml \cdot h^{-1}$. There was no significant difference in the plasma lidocaine concentrations over 120 min after initial injection of lidocaine between the two groups. However, the concentration at 180 min after initial injection in the PGE_1 group was significantly lower than that in the control group ($p < 0.05$). The maintained hepatic blood flow by PGE_1 may contribute to this result.

Key words ; Plostaglandin E_1, Plasma lidocaine concentration, Epidural blockade.

Introduction

Because the major part of lidocaine injected into the epidural space is absorbed through the epidural vessels and degraded in the liver, hepatic blood flow plays an important role for a determination of plasma lidocaine concentration[1]. Therefor, there is a possibility that plasma lidocaine concentration increases due to reduction in hepatic blood flow during abdominal surgery[3,4]. Previous study suggested that intravenous (IV) administration of prostaglandin E_1 (PGE_1) produces an increase in hepatic blood flow[5]. We hypothesized that if PGE_1 maintains hepatic blood flow during epidural blockade, then it will affect lidocaine concentrations. Hence, we administered PGE_1 in patients who underwent lower abdominal surgery and evaluated the changes in the plasma concentrations of lidocaine.

Materials and Methods

The protocol of this study was approved by our ethics committee, and informed consent was obtained from each patient. The subjects were 14 adult female patients of ASA physical status 1 who had been scheduled for major gynecologic surgery whose operating time was expected over 3 hr. Patients with hepatic or cardiopulmonary disorders were excluded.

Preanesthetic medications consisted of 2.0-2.5 mg of midazolam and 0.5 mg of atropine injected intramuscularly 1h before arrival to the operating room. A 18-gauge IV catheter was placed for infusion of lactated Ringer's solution at 8-10 $ml \cdot kg^{-1} \cdot hr^{-1}$ during the study.

For the patient in the lateral position, a catheter was inserted 5 cm directed cephalad through a 16-gauge Tuohy needle into the epidural space at the L2-3 or L3-4 interspace after infiltrations of skin and para-

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vertebral structures with 1 % mepivacaine. The epidural space was identified using the loss of resistance method. The catheter was aspirated carefully to exclude the intrathecal or intravascular placement.

The anesthesia was induced with thiamylal (3 mg·kg^{-1} IV) followed by vecuronium (0.1 mg·kg^{-1} IV). After orotracheal intubation the anesthesia was maintained with 0.5 % isoflurane in 2 l·min^{-1} oxygen and 4l·min^{-1} nitrous oxide. Incremental doses of vecuronium 2 mg were given IV when required throughout surgery. Ventilation was controlled mechanically to maintain the end-tidal carbon dioxide concentration at 35–40 mmHg. A radial arterial catheter was inserted for continuous monitoring of arterial blood pressure and collection of blood samples.

Shortly after the intubation, 1.5 % plain lidocaine was injected through the epidural catheter as a 10 ml loading bolus, followed by continuously administration of 8 ml·hr^{-1} during surgery. Patients were divided into two groups at random. In the PGE_1 group (n=7), 0.02 μg·kg^{-1}·min^{-1} of PGE_1 was infused after the induction of anesthesia until the end of surgery. In the control group (n=7), patients were not given PGE_1.

Blood samples (5 ml) were collected at 20, 40, 60, 120, and 180 min after the initial injection of lidocaine. Plasma was separated by centrifugation (3000 rpm), and kept at −40℃ until the analysis. The plasma lidocaine concentrations were measured by a high performance liquid chromatography system (pump : HLC-803D, TOSOH, Tokyo, Japan) set at 230 nm. A computing integrator (Chromatopack C-RIA, Shimazu Corporation, Kyoto, Japan) was used to calculate the peak area. The mobile phase was constituted of acetonitrile and 0.05 mol/sodium phosphate buffer (29 : 71, v/v, pH 3.3); flow rate 0.6 m/min. The reversed column was μ Bondashere 5 μ C8-100A (3.9 mm×15 cm). The coefficient of variation of measured lidocaine concentration by C18 Sep-Pak method was 2.0–9.0 % and the recovery of lidocaine was 65–71 % over a concentration range of 0.2–5.0 μg·ml^{-1}.

Mean arterial pressure (MAP) and heart rate (HR) were measured continuously and recorded. The estimated blood loss, urinary output, amount of infused lactated Ringer's solution, and the cumulative dose of ephedrine during surgery were recorded. Hypotension was defined as a systolic arterial pressure (SAP) <90 mmHg or a decrease in SAP >30 % of preanesthetic value, and was treated with 5–10 mg of ephedrine IV.

Results were expressed as mean ± SD. Statistical analysis was performed by Student's T-test. A p value <0.05 was considered to be significant.

Table1 Patient characterictics and clinical features

	PGE_1 group (n = 7)	Control group (n = 7)
Age (years)	51.5± 13.7	42.8± 12.5
Weight (kg)	59.5± 10.5	54.8± 9.0
Height (cm)	157.3± 3.9	154.6± 3.4
Duration of operation (min)	225 ± 32	212 ± 26
Blood loss (g)	512 ±255	441 ±198
Urine volume (ml)	165 ± 72	174 ± 80
Infusion (ml)	2170 ±475	2275 ±319
Ephedrine (mg)	8.0± 3.1	7.5± 2.0

Values are mean ± SD.

Results

Both groups were comparable for patients' characteristics, estimated blood loss, urinary output, volume of infused lactated Ringer's solution, and dose of ephedrine during the study (Table 1).

There was no significant difference in HR between the two group. MAP was decreased after the epidural injection of lidocaine in both groups, but these changes were not significant. No significant difference between the two groups was noted in MAP (Fig.1). SAP was maintained over 90 mmHg throughout the study.

Differences in the plasma lidocaine concentrations at 20, 40, 60, 120 min after the initial injection of lidocaine were no significant between two groups. However, the concentration at 180 min after the initial injection in the PGE_1 group was significantly lower than that in the control group (Fig.2). There was no case whose concentration was abnormally high.

Discussion

The present study demonstrated that the infusion of PGE_1 suppresses the increase in the plasma concentrations of lidocaine in patients undergoing gynecologic

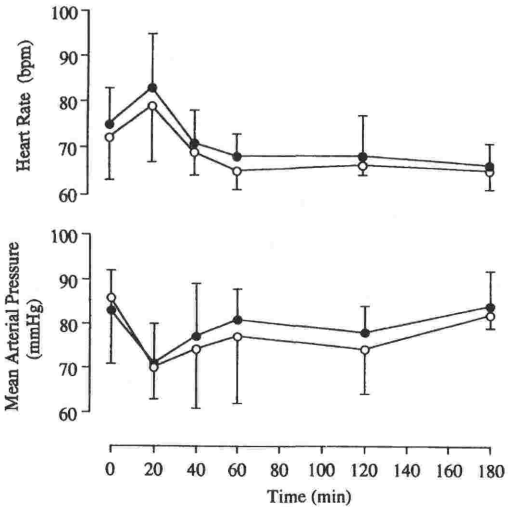

Fig 1. Changes in heart rate and mean arterial pressure(during measurement). Values are mean ±SD. Open circles ; PGE_1 group, closed circles ; control group.

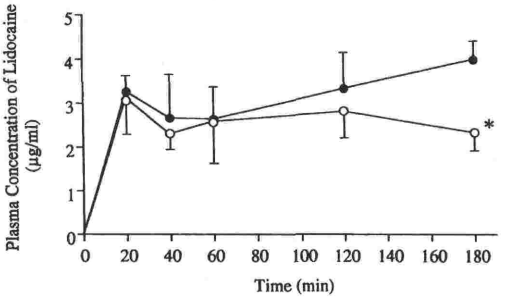

Fig 2. Changes in plasma lidocaine concentration(during measurement). Values are mean ±SD. Open circles ; PGE_1 group, closed circles ; control group.
*P<0.05versus control group.

surgery under epidural blockade plus general anesthesia.

Because approximately 70 % of lidocaine is eliminated from the blood after a single circulation through the liver, hepatic circulatory disturbance reduces the clearance of plasma lidocaine[1]. Several factors, such as surgical procedures, anesthetic agents, and mechanical ventilation, affect hepatic circulation during surgery[6]. Surgical stress induces the release of various hormones and substances which impair hepatic circulation[7]. Laparotomy causes mesenteric vasoconstriction and disturbs the splanchnic circulation[6-8]. Gelman and co-workers[3,4,6] described that laparotomy is associated with a profound decrease in hepatic blood flow. Therefore, there is possibility that the plasma lidocaine concentrations increased unexpectedly in some patients undergoing laparotomy by the reduction in hepatic blood flow. The study from our laboratory showed that the plasma concentrations of lidocaine increase significantly during hepatectomy[9].

A low dose PGE_1 has been reported to maintain organ blood flow, despite a drop in systemic arterial pressure[10]. PGE_1 acts directly on the vascular smooth muscle and increases hepatic blood flow[5]. Thus, it can be speculated that PGE_1 may improve the clearance of drugs whose systemic elimination is dependent on hepatic blood flow. Takasaki et al.[11] described that the plasma bupivacaine concentration decreases more rapidly during PGE_1 induced hypotension than during trimetaphan induced hypotension. Our study revealed that the increase in the plasma concentration of lidocaine is suppressed by a low dose administration of PGE_1.

In this study, the difference in the plasma lidocaine concentrations between two groups was found only at 180 min after the initial injection. We do not know this reason, but, prolonged surgical stress might induced significant reduction in hepatic blood flow and the lidocaine clearance in the control group. We administrated lidocaine continuously because intermitted injection of local anesthetics into the epidural space is reported to cause the crenate increasing of the plasma concentrations[12] which makes it difficulty to measure the proper concentrations.

Hemodynamic alternation is one of the major determinations of hepatic blood flow. Although epidural or spinal anesthesia decreases hepatic blood flow in parallel with a decrease in arterial blood pressure, these reductions can be attenuated by ephedrine administration[13,14]. In this study, we used ephedrine to maintain the arterial blood pressure and the total doses of ephedrine was comparable between two groups. Thus, systemic hemodynamic changes induced by epidural anesthesia appear to have little effect on hepatic circulation to contribute to our result.

In conclusion, a low dose of PGE_1 suppresses the increase in the plasma concentrations of lidocaine in patients undergoing gynecologic surgery under epidural blockade. The maintained hepatic blood flow during laparotomy by PGE_1 may contribute to this finding.

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