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Comparison of renal function under deliberate hypotension during epidural plus light-enflurane anesthesia and during enflurane anesthesia

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Abstract: We compared the effects of deliberate hypotension induced with trimethaphan on renal function and renal tubular damage under combined epidural and light-enflurane anesthesia (epidural group) and enflurane anesthesia alone (enflurane group). The mean arterial blood pressure was maintained at 50–55 mmHg for 2.5 h in both groups using continuous infusion of trimethaphan. The urine volume and free water clearance were significantly greater in the epidural group than in the enflurane group [1.8 ± 1.8 (SD) *vs* 0.4 ± 0.3 ml·kg^{-1}·h^{-1} and 0.81 ± 1.30 *vs* −0.15 ± 0.22 ml·min^{-1}, respectively] ($P < 0.05$). The creatinine clearance and fractional sodium excretion rate did not differ significantly between the two groups. Urinary excretion of norepinephrine was significantly less in the epidural group than in the enflurane group ($P < 0.05$); however, epinephrine excretion did not differ. Urinary excretion of *N*-acetyl-β-D-glucosaminidase was significantly less in the epidural group than in the enflurane group (4.2 ± 2.5 *vs* 12.2 ± 4.6 U·g^{-1} CR) ($P < 0.01$). The plasma antidiuretic hormone concentration was significantly lower in the epidural group compared to the enflurane group (13 ± 23 *vs* 57 ± 42 pg·ml^{-1}) ($P < 0.05$). No significant difference in plasma atrial natriuretic peptide concentration was found between the groups. We conclude that renal function during trimethaphan-induced hypotension is better maintained under epidural plus light-enflurane anesthesia than under enflurane anesthesia alone.

Key words: Epidural anesthesia, Deliberate hypotension, Renal function

Introduction

Deliberate hypotensive anesthesia is useful to reduce intraoperative blood loss and to obtain a bloodless surgical field [1,2]. Although various techniques are available for hypotensive anesthesia, intravenous administration of vasodilators under inhalation anesthesia is most commonly practiced. Epidural anesthesia induced by continuous infusion of local anesthetics maintains blood pressure at a lower level without fluctuation by surgical stimulation, and provides deliberate hypotension easily by continuous infusion of a low dose of vasodilators [3]. Epidural block under light general anesthesia is even easier than epidural block alone to maintain blood pressure at a lower level and to avoid nausea and anxiety during hypotension [4]. However, this anesthetic method suppresses the compensatory vasoconstriction response to fluid loss and reduces cardiac output due to bradycardia during hypotension [5,6]. Profound or prolonged hypotension may cause ischemia to tissues and organs. The kidney is easily injured by hypoperfusion [7]. Renal tubular cell injury caused by deliberate hypotension induced by epidural anesthesia and vasodilators has not been studied. The present study was designed to evaluate whether prolonged hypotensive anesthesia induces renal dysfunction or renal tubular injury, and whether adverse effects associated with deliberate hypotension under general anesthesia differ from those under epidural plus light general anesthesia.

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Patients and methods

Patients

This study was approved by our institutional human investigation committee, and written informed consent was obtained from each patient. Twenty-four adult patients with ASA physical status I or II, scheduled for elective spherical acetabular osteotomy to treat osteoarthritis of the hip joint under hypotensive anesthesia, were studied. Hypotensive anesthesia was frequently carried out in this operation to reduce intraoperative blood loss. The patients were randomly

divided into two groups: an epidural group and an enflurane group of 12 patients each. All patients had 1000–1600g each of autologous blood stored preoperatively to prevent homologous blood transfusion. They had no cardiovascular or renal abnormality.

Anesthesia

All patients were premedicated with 0.8mg of brotizolam orally 2h before induction of anesthesia, and 25mg of hydroxyzine and 0.5mg of atropine intramuscularly 30min before induction of anesthesia. Ringer's lactated solution was infused at a rate of $10ml \cdot kg^{-1} \cdot h^{-1}$ in both groups. A 22-gauge nontapered Teflon cannula (Surflo, Termo, Tokyo, Japan) was inserted into the left radial artery for blood sampling and blood pressure monitoring. Patients were laid supine on an operating table.

A catheter was inserted into the epidural space and advanced in a cephalad direction at the L3–L4 interspace. According to age and height, 10–15ml of 2% meptivacaine solution without epinephrine was injected as an initial volume 5min after injection of 4ml of 2% mepivacaine as a test dose in the epidural group. The upper level of blockade extended to an average of T6 as assessed by cold and T8 by pin-prick 15min after the initial injection. Then, 2% mepivacaine without epinephrine was infused continuously through the epidural catheter at a rate of $8–10ml \cdot h^{-1}$ using a syringe infusion pump (STC-525, Termo, Tokyo, Japan) to avoid fluctuation of blood pressure and excess elevation of the blood mepivacaine level [8]. In the enflurane group, no local anesthetics were injected during surgery. The epidural catheter was used for postoperative pain relief in the both groups.

General anesthesia was induced with $5mg \cdot kg^{-1}$ of thiamylal, and $0.1mg \cdot kg^{-1}$ of pancuronium bromide was given to facilitate tracheal intubation in all patients. Anesthesia was maintained with 0.2%–0.3% enflurane and 67% nitrous oxide in oxygen following intravenous injections of 10mg of diazepam and 15mg of pentazocine to avoid tracheal stimulation and awareness in the epidural group. In the enflurane group, anesthesia was maintained with 1.8%–2.0% enflurane and 67% nitrous oxide in oxygen. Ventilation was controlled using a volume-cycled ventilator (Ohmeda 7000, Ohmeda, Liberty-corner, NJ, USA) at a rate of $10–15 \cdot min^{-1}$, a tidal volume of $6ml \cdot kg^{-1}$ and an I/E ratio of 0.5, to maintain normocapnia. The end-tidal carbon dioxide and enflurane concentrations were determined by capnography (Capnomac Ultima SV, Datex, Helsinki, Finland).

Hypotension was induced before surgery and maintained until the end of surgery in the two groups. The systolic and mean radial artery pressures were reduced to 70–80mmHg and 50–55mmHg, respectively, by continuous intravenous infusion of trimethaphan (TMP) and were maintained at these levels for more than 2.5h by controlling the infusion rate of TMP ($10–80\mu g \cdot kg^{-1} \cdot min^{-1}$). During surgery, when the estimated intraoperative blood loss was 300–400ml, 400ml of autologous blood was transfused in each patient. The systolic radial artery pressure was restored to 100–110mmHg at the end of anesthesia by discontinuation of TMP. Residual autologous blood was given postoperatively.

After surgery, 1l of Ringer's lactated solution and 0.5–1.0l of maintenance solution (Na 35, K 20, Cl 35, lactate $20mEq \cdot l^{-1}$ in 7.5% glucose) were administered until the next morning. The 1st postoperative day, the patients were permitted to take food and drink orally without intravenous infusion of maintenance solution. To prevent infection, 1g of cefotiam dihydrochloride was infused with 100ml of normal saline every 12h for 1 week.

Sampling and analysis

A 24-h urine volume was sampled at 1 day before and after surgery. During hypotension, urine samples were collected for 2h from 30min after the start of operation. Five ml of blood was sampled at 1 day before and after surgery, and at 1.5h after the start of hypotension. For measurements of antidiuretic hormone (ADH) and atrial natriuretic peptide (ANP) concentrations, 10-ml blood samples were collected into test tubes containing ethylene diamine tetraacetate (EDTA) and aprotinin before induction of anesthesia, during hypotension (at 1.5h after the start of hypotension), and at the end of anesthesia.

Urinary and plasma osmotic pressures were measured with an automatic semimicro osmometer (DISMO, Knauer, Berlin, Germany), and the free water clearance (C_{H_2O}) was calculated from these values and urine volume. Urinary and plasma creatinine (CR) concentrations were measured with a spectrophotometer by the Jaffé reaction [9]. The creatinine clearance (Ccr) was calculated from urinary and plasma CR and urine volume (UV). Ccr and C_{H_2O} were standardized by body surface. Sodium (Na) concentration was measured using an ionselective electrode (NOVA 1 sodium/potassium analyzer), and the fractional sodium excretion (FE_{Na}) was calculated from the urinary and plasma Na and CR concentrations. Epinephrine and norepinephrine concentrations were measured by high-performance liquid chromatography (HLC-825 CA, Tosoh, Tokyo, Japan). This assay system is based on the trihydroxyindol reaction, and has sensitivity limits of $5pg \cdot ml^{-1}$ for epinephrine and $30pg \cdot ml^{-1}$ for norepinephrine. Urinary epinephrine and norepinephrine were expressed as $pg \cdot g^{-1}$ CR to eliminate the effect of

UV differences [10]. Assay of *N*-acetyl-β-D-glucosaminidase (NAG) was performed by the NAG activity estimation method with sodio-m-cresolsulfonphthaleinyl-*N*-acetyl-β-D-glucosaminide employing a commercial kit (Shionogi, Osaka, Japan) [11]. Because enzyme activity is related to urinary CR excretion, the results were expressed as an NAG index ($U \cdot g^{-1}$ CR) to correct the differences in UV. For measurements of ADH and ANP, the blood samples were subjected to radioimmunoassay [12,13]. The lower limit of ANP detection in this assay was $1 pg \cdot ml^{-1}$. ADH was measured by radioimmunoassay after further separation of ADH from plasma extracts by immunoaffinity chromatography using the IgG fraction of anti-ADH antiserum [14], which had a sensitivity limit of $0.1 pg \cdot ml^{-1}$.

Statistical analysis

Within each group, the results of the repeated measurements were analyzed by analysis of variance (ANOVA) for repeated measures and then, where appropriate, followed by Scheffe's test as a multiple comparison procedure. Comparison between the two groups was carried out by Studen's *t*-test or the Mann-Whitney test for unpaired data. $P < 0.05$ was considered statistically significant. The data were expressed as mean ± SD.

Results

There were no statistically significant differences between the two groups in patient profiles (Table 1). The amount of TMP infused during hypotensive anesthesia was 117 ± 77 mg and 106 ± 90 mg in the epidural and enflurane groups, respectively. The hypotensive drug administered was the same in both groups. The volume of stored autologous blood before surgery and the blood losses both during hypotension and surgery and after surgery were not significantly different between the two groups (Table 2). The mean volume of autologous blood transfused during hypotension did not differ significantly between the two groups, not did the mean volume of Ringer's lactated solution infused during surgery.

Table 1. Patient profiles

	Epidural group	Enflurane group
No. of patients	12	12
Sex (M:F)	1:11	0:12
Age (yr)	36 ± 12	40 ± 14
Weight (kg)	51 ± 9	52 ± 6
Height (cm)	153 ± 6	152 ± 4

Values are mean ± SD.

Table 2. Stored autologous blood and blood losses

	Epidural group	Enflurane group
Stored autologous blood (ml)	1241 ± 306	1217 ± 103
Blood loss during hypotension (ml)	516 ± 206	493 ± 145
Blood loss during surgery (ml)	602 ± 297	534 ± 164
Blood loss after surgery (ml)	466 ± 220	361 ± 139

Values are mean ± SD.

Table 3. Renal function during controlled hypotension

	Epidural group	Enflurane group
Urine volume ($ml \cdot kg^{-1} \cdot h^{-1}$)	1.8 ± 1.8*	0.4 ± 0.3
Free water clearance ($ml \cdot min^{-1}$)	0.81 ± 1.30*	−0.15 ± 0.22
Creatinine clearance ($ml \cdot min^{-1}$)	64 ± 23	41 ± 27
Fractional sodium excretion (%)	0.60 ± 0.45	0.52 ± 0.31

Values are mean ± SD.
* $P < 0.05$ compared with enflurane group.

The mean arterial blood pressure in the epidural and enflurane groups was 89 ± 9 and 89 ± 11 mmHg before anesthesia; 57 ± 3 and 58 ± 3 mmHg 30 min after anesthesia; 53 ± 2 and 53 ± 3 mmHg 100 min after hypotension; and 79 ± 6 and 88 ± 10 mmHg after surgery, respectively. There was a significant difference between the two groups in the values after surgery ($P < 0.05$). The heart rate in the epidural and enflurane groups was 92 ± 15 and 91 ± 17 $\cdot min^{-1}$ before anesthesia; 70 ± 9 and 79 ± 10 $\cdot min^{-1}$ 30 min after anesthesia; 66 ± 6 and 80 ± 10 $\cdot min^{-1}$ 100 min after hypotension; and 82 ± 8 and 76 ± 7 mmHg after surgery, respectively. There was a significant difference between the two groups in the values during hypotension ($P < 0.05$).

The mean UV during hypotension was significantly greater in the epidural group than in the enflurane group ($P < 0.05$) (Table 3). The mean C_{H_2O} was significantly larger in the epidural group than in the enflurane group ($P < 0.05$). Ccr at 1 day before surgery was 89 ± 30 $ml \cdot min^{-1}$ and 91 ± 32 $ml \cdot min^{-1}$ in the epidural and enflurane groups, respectively. In the two groups, Ccr decreased significantly during hypotension ($P < 0.05$), compared with the values at 1 day before surgery, but there was no difference between the two groups. Ccr and UV recovered to preoperative values at 1 day after surgery in the two groups. The mean FE_{Na} during

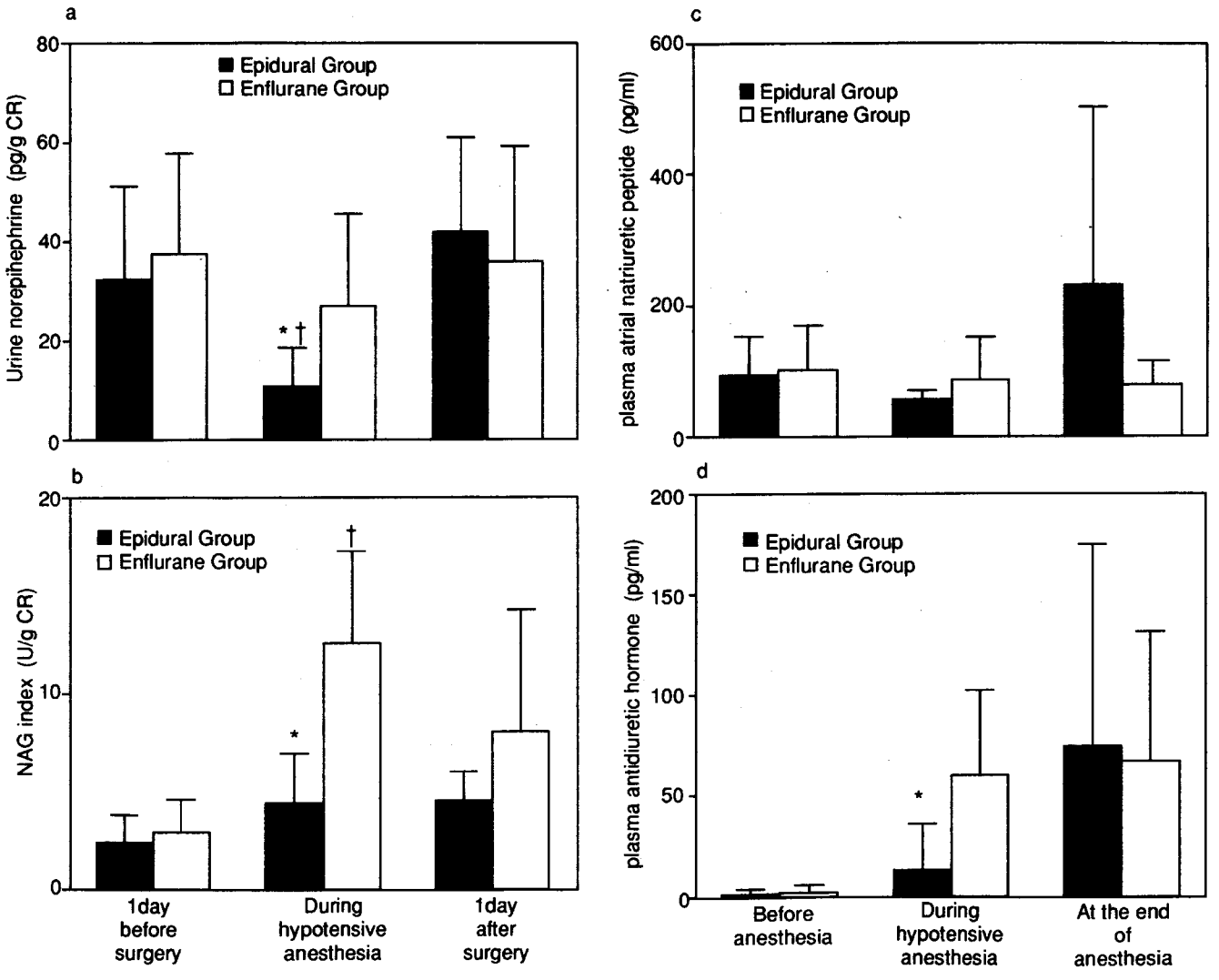

Fig. 1. a Urinary excretion of norepinephrine during perioperative period in epidural (*solid bars*) and enflurane (*open bars*) groups. Values represent mean ± SD. $*P < 0.05$ compared with enflurane group. $^{\dagger}P < 0.05$ compared with the value at 1 day before surgery. **b** *N*-acetyl-β-D-glucosaminidase (NAG) index during perioperative period in epidural and enflurane groups. Values represent mean ± SD. $*P < 0.01$ compared with enflurane group. $^{\dagger}P < 0.05$ compared with the value at 1 day before surgery. **c** Plasma atrial natriuretic peptide concentrations during perioperative period in epidural and enflurane groups. Values represent mean ± SD. **d** Plasma antidiuretic hormone concentrations during perioperative period in epidural and enflurane groups. Values represent mean ± SD. $*P < 0.05$ compared with enflurane group

hypotension did not differ significantly between the two groups. During the perioperative period, the urinary excretion of epinephrine was not significantly different between the two groups. However, the urinary excretion of norepinephrine during hypotension was significantly lower in the epidural group than in the enflurane group ($P < 0.05$) (Fig. 1). The mean ADH concentration during hypotension was significantly lower in the epidural group than in the enflurane group ($P < 0.05$), but at the end of anesthesia no difference was seen between the two groups. The mean NAG index (normal value is 3.3 ± 1.6 $U \cdot g^{-1}$ CR [15]) increased significantly during hypotension in the enflurane group, as compared with the value at 1 day before surgery ($P < 0.05$). In the epidural group, the NAG index did not increase, and a significant difference was observed between the two groups during hypotension ($P < 0.01$).

The mean ANP concentration remained unchanged in the enflurane group, but in the epidural group it increased after surgery. Aspartate aminotransferase was within a normal limit at day 7 after surgery in all patients. Renal or hepatic dysfunction was not observed in any patients on discharge.

Discussion

This study demonstrated that renal function was better maintained during hypotensive anesthesia induced by the combination of epidural plus enflurane anesthesia and TMP than during that induced by enflurane anesthesia and TMP. The use of epidural block during deliberate hypotension maintained the osmotic regulation of the kidney, because C_{H_2O} remained within a normal limit and UV increased above $1\,ml \cdot kg^{-1} \cdot h^{-1}$ in spite of prolonged hypotension for 2.5h with mean arterial blood pressure at 50–55mmHg in the epidural group.

In the epidural group of our study, the lower urinary norepinephrine and the lower plasma ADH concentrations indicated that epidural block suppressed ADH hypersecretion and norepinephrine release induced by nociceptive stimuli from the operating area. As a result, UV during hypotension was maintained because free water was not absorbed in the renal distal portion by ADH.

The upper level of analgesia was T8; therefore, the upper level of sympathetic nerve block appears to be T5 or T6 after induction of epidural anesthesia [16,17]. However, during hypotension, the sympathetic nerve block may have been above T5, as shown by the appearance of bradycardia in the epidural group. No activation of renal sympathetic nerves (T6-L2) and no constriction of renal arteries occurred during epidural anesthesia [18]. Gamulin et al. [19] compared renal function and hemodynamic variables before and during aortic cross-clamp in patients with and without sympathetic blockade. They suggested that lumbar epidural block provides renal protection against surgical and hypotensive stresses, because high preclamp values of renal perfusion and function are attributed to the interruption of renal sympathetic outflow.

NAG is the most widely used urinary enzyme to evaluate renal tubular injury [14]. In the enflurane group, the NAG index increased significantly during hypotension. A significant difference in the NAG index between the two groups was not associated with hemodynamics. In our previous study [20], the cardiac index during hypotension with a mean arterial pressure of 50–55mmHg was similar in enflurane anesthesia and in epidural plus general anesthesia. In our previous in vivo ischemic model of complete renal artery occlusion [21], NAG represented an early sensitive index of injury of renal tubular cells, as compared with a significant decrease in Ccr. In the enflurane group of this study, renal tubular cells were transiently injured. Akabane et al. [22] reported that the urinary excretion of NAG markedly increased with a decrease in renal blood flow which was caused by acute abdominal aortic occlusion or intrarenal norepinephrine infusion in anesthetized dogs. In our study, the increase in NAG could have resulted from the slight reduction of intrarenal blood flow caused by the sympathetic and endocrine responses to surgery and hypotension during enflurane anesthesia without a decrease in Ccr, although enflurane itself is not directly toxic to renal tubular cells [23].

The plasma ANP level during hypotension was not changed in the two groups, but at the end of anesthesia it increased in the epidural group. When the effect of epidural block disappears and peripheral vessels are constricted, the atrial pressure increases and then the plasma ANP level increases [24]. The amount of TMP used in our study was similar in the two groups. We speculated that a normally prescribed dose of TMP was required to dilate blood vessels constricted by overactivated sympathetic nerves in the epidural group, because epidural anesthesia leads to blood pooling in the denervated lower extremities but causes reflex vasoconstriction in the innervated arm [25].

In conclusion, epidural block maintains better renal function during trimethaphan-induced hypotension under light-enflurane anesthesia, compared with that obtained during trimethaphan-induced hypotension under enflurane anesthesia.

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