Lumbar epidural anaesthesia prevented prostaglandin E_1-induced diuretic effect in enflurane anaesthetized patients

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Prostaglandin E_1 (PGE_1) is used to induce deliberate hypotension during anaesthesia. The purpose of this study was to compare the PGE_1-induced diuretic effect in anaesthetized patients with and without lumbar epidural anaesthesia. The changes in haemodynamic variables, urinary flow, one-hour creatinine clearance (Ccr), and fractional excretion of sodium (FE_{Na}) during injection of PGE_1 or a vehicle were compared in 42 surgical patients during enflurane anaesthesia with lumbar epidural anaesthesia (EPI group) with those in 44 surgical patients during enflurane anaesthesia alone (GA group). Patients in the GA group demonstrated increases in urinary flow (114 ± 46%) (mean ± SE), Ccr (74 ± 26%), and FE_{Na} (54 ± 23%) during PGE_1 infusion, which were not observed in the patients in the EPI group. Mean arterial pressure decreased during PGE_1 infusion from 92 ± 3 to 70 ± 2 mmHg in the GA group ($P < 0.01$) and from 85 ± 2 to 65 ± 1 mmHg in the EPI group ($P < 0.01$). Plasma antidiuretic hormone concentration during surgery was 12.5 ± 2.6 $U \cdot L^{-1}$ in the GA group and 2.3 ± 0.8 $U \cdot L^{-1}$ in the EPI group ($P < 0.001$). It is concluded that PGE_1-induced diuresis was prevented by lumbar epidural anaesthesia.

La prostaglandine E_1 (PGE_1) est utilisé en anesthésie pour induire une hypotension contrôlée. L'objectif de cette étude est de comparer l'effet diurétique induit par la PGE_1 chez les patients anesthésiés avec et sans anesthésie épidurale lombaire. Pendant la perfusion de la PGE_1 ou bien celle d'un soluté inactif, on a comparé les modifications de variables hémodynamiques, du débit urinaire, de la clairance horaire de la créatinine (Ccr) et de la fraction excrétée du sodium (FE_{Na}) entre un groupe de 42 patients opérés sous enflurane en plus d'une anesthésie épidurale lombaire (groupe EPI) et un groupe de 44 patients sous enflurane seul (groupe AG). Les patients dans le groupe AG ont eu une augmentation significative du débit urinaire (114 ± 46%) (moyenne ± erreur-type), de Ccr (74 ± 26%) et de FE_{Na} (54 ± 23%) pendant la perfusion de PGE_1, augmentation non observée chez les patients du groupe EPI. La pression artérielle moyenne a diminué pendant la perfusion de PGE_1 de 92 ± 3 à 70 ± 2 mmHg dans le groupe GA ($P < 0.01$) et de 85 ± 2 à 65 ± 1 mmHg dans le groupe EPI ($P < 0,01$). La concentration plasmatique de l'hormone antidiérutique pendant la chirurgie a été de 12,5 ± 2,6 $U \cdot L^{-1}$ dans le groupe GA et de 2,3 ± 0,8 $U \cdot L^{-1}$ dans le groupe EPI ($P < 0,001$). Il est conclu que la diurèse induite par la PGE_1 est prévenue par l'anesthésie épidurale lombaire.

Key words
ANAESTHETIC TECHNIQUES: hypotension, epidural;
HORMONES: prostaglandins;
KIDNEY: diuresis.

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Deliberate hypotension is commonly carried out, especially during neurosurgical and orthopaedic procedures, to reduce blood loss, thereby decreasing the need for blood transfusion, and keeping a dry operative field.[1] However, depending on the drugs used, hypotension may have some disadvantages such as a transient decrease of renal function[2] and an increase in intracranial pressure.[3,4] Prostaglandin E_1 (PGE_1) is widely used to produce de-

liberate hypotension[1,5] whilst maintaining renal perfusion.[6]

The increase in urinary flow produced by PGE_1 is via two mechanisms; the release or dilatation of the renal arteries from the constriction induced by surgical stress, endogenous cathecolamines and/or angiotensin,[7] and an increase in urinary sodium excretion,[8,9] via the renal distal tubulus in the presence of increased plasma antidiuretic hormone (ADH) concentration.[10-13] In patients undergoing surgery with lumbar or thoracic epidural anaesthesia using local anaesthetic, plasma cathecolamine and ADH concentrations are suppressed[14,15] and lumbar and thoracic sympathetic activity is blocked, resulting in decreased systemic blood pressure and decreased renal perfusion.[16] Therefore, PGE_1 may not produce a diuretic effect in patients undergoing surgery with epidural anaesthesia.

The purpose of this study was to compare the PGE_1-induced diuretic effect in patients undergoing surgery with general anaesthesia with or without epidural anaesthesia.

Methods

The study protocol was approved by the ethical committee, Department of Anesthesiology, Institute of Clinical Medicine, University of Tsukuba, Japan. Ninety-six patients, who were scheduled for major elective surgery during the period from October, 1989, to May, 1990, in University of Tsukuba Hospital, were enrolled in this study. They included patients undergoing lower abdominal or extremity (hip or femoral) surgery in the supine position. The surgery started in the morning and took more than three hours. Written informed consent was obtained from each patient. Patients were randomly assigned into two groups. The epidural (EPI) group consisted of 47 patients who received general anaesthesia combined with lumbar epidural anaesthesia, and the general anaesthesia (GA) group consisted of the remaining 49 patients who received general anaesthesia alone. Patients in each group were further divided at random into two subgroups; namely, prostaglandin (PG) and sham control (C) subgroups. Patients with diabetes mellitus and/or renal insufficiency (serum creatinine level > 1.5 $mg \cdot dL^{-1}$), and those whose intraoperative urine flow before the infusion period was less than 0.5 $ml \cdot kg^{-1} \cdot hr^{-1}$ were excluded from the study.[17]

Each patient was NPO from the previous midnight until the time of surgery. Lead II of the ECG was monitored continuously and arterial blood pressure and heart rate were determined every five minutes using either a noninvasive oscillometer (BP-308™, Nippon Colin, Japan) or via a radial arterial catheter via a transducer and an appropriate amplifier (Monitoring Kit™, Baxter, U.S.A., and Bioview™, NEC Sanei, Japan). Lactated Ringer's solution was infused at the rate of 15 $ml \cdot kg^{-1}$ for the first hour followed by 8–15 $ml \cdot kg^{-1} \cdot hr^{-1}$. In all patients, anaesthesia was induced with thiamylal, 4 $mg \cdot kg^{-1}$, *iv*, tracheal intubation was facilitated with vecuronium, 0.2 $mg \cdot kg^{-1}$, *iv*, and anaesthesia was maintained using enflurane 0.5 to 1.5% inspired, nitrous oxide 67%, and oxygen and controlled ventilation. Hypotension and hypertension during the study were treated by adjusting the *iv* fluid infusion rate and/or anaesthetic level.

In the EPI group, before induction of general anaesthesia, each patient received a lumbar epidural catheter placement via the $L_{1/2}$ interspace. Epidural anaesthesia was accomplished using lidocaine 1.5% with 1:200,000 epinephrine, in an initial dose of 12 to 15 ml followed by an infusion, 6 $ml \cdot hr^{-1}$. The level of lumbar epidural anaesthesia obtained 15 min after the initial dose was T_4 to T_6.

The PGE_1 solution was prepared in a 50 ml syringe to a concentration of 10 $\mu g \cdot ml^{-1}$. A control solution without PGE_1 was also prepared. Beginning 30 min after the start of surgery, a precise one-hour urine collection was made, and, after the collection, arterial blood was drawn for blood gas analysis (pHa, PaO_2 and $PaCO_2$), and serum creatinine and sodium, and plasma antidiuretic hormone (ADH) concentrations determination. The bladder was emptied either by compressing the suprapubic area or by the surgeon squeezing the bladder directly before and at the end of the one-hour urine collection.[26] Next, patients received PGE_1 (in EPI-PG and GA-PG subgroups) or control solution (in EPI-C and GA-C subgroups) infused at a rate of 0.3 · (body weight in kg) $ml \cdot hr^{-1}$ (50 $ng \cdot kg^{-1} \cdot min^{-1}$ in PG subgroups). After blood pressure and heart rate became stable, 20 min after the start of infusion, a second one-hour urine collection was made. Then, the infusion of PGE_1 or vehicle was stopped. The anaesthetist was unaware of which solution had been infused.

Serum and urinary creatinine and sodium concentrations were determined for each urine sample by a SX discrete clinical analyzer, Dupont, U.S.A. and NOVA6 Electrolyte analyzer, NOVA Biomedical, U.S.A., respectively. Minute urine flow, creatinine clearance (Ccr), and the fraction of excretion of sodium (FE_{Na}) were calculated for each urine sample[18] using the formulas shown below.

$$Ccr = \frac{U\text{–}Cr * \text{one-hour urine volume}}{S\text{–}Cr * 60} (ml \cdot min^{-1}).$$

where

U–Cr: urinary creatinine concentration,
S–Cr: serum creatinine concentration.

$$FE_{Na} = \frac{U\text{–}Na * S\text{–}Cr}{S\text{–}Na * U\text{–}Cr} * 100\ (\%)$$

TABLE I Demographic data

Subgroup	*EPI-PG*	*EPI-C*	*GA-PG*	*GA-C*
n	22	20	23	21
(M/F)	(13/9)	(9/11)	(14/9)	(5/16)
Age (yr)	52 ± 2	52 ± 3	48 ± 4	45 ± 4
Height (cm)	161 ± 2	160 ± 2	154 ± 2	150 ± 2*
Weight (kg)	54 ± 2	61 ± 3†	57 ± 2	54 ± 2
$PaCO_2$ (mmHg)	34 ± 1	33 ± 1	33 ± 1	35 ± 1
PaO_2 (mmHg)	161 ± 6	157 ± 6	154 ± 2	150 ± 1
IV-F ($ml \cdot kg^{-1} \cdot hr^{-1}$)	15.2 ± 1.0	13.0 ± 1.0	12.7 ± 1.1	11.0 ± 1.0‡
PGE_1 ($ng \cdot kg^{-1} \cdot min^{-1}$)	50	0	50	0

Mean ± SE.
*$P < 0.05$ vs other three subgroups. †$P < 0.05$ vs EPI-PG and GA-C subgroups; ‡$P < 0.05$ vs EPI-PG subgroup.
IV-F: mean volume of lactated Ringer solutions infused during the study period.
PGE_1: mean infusion rate of prostaglandin E_1.

TABLE II Haemodynamic data

	Before-infusion	*During-infusion*	*After-infusion*
MAP (mmHg)			
EPI-PG	85 ± 2	65 ± 1*	84 ± 1
EPI-C	82 ± 2	81 ± 2	81 ± 2
GA-PG	92 ± 3	70 ± 2*	87 ± 3
GA-C	84 ± 2	82 ± 2	84 ± 2
HR (bpm)			
EPI-PG	77 ± 3	80 ± 4	77 ± 3
EPI-C	72 ± 2	73 ± 3	73 ± 3
GA-PG	75 ± 3	91 ± 3*	82 ± 3
GA-C	80 ± 3	80 ± 3	82 ± 3

Mean ± SE.
No significant differences in Before-infusion values among the four subgroups. MAP: mean arterial pressure; HR: heart rate.
*$P < 0.01$ vs Before-infusion value.

where

S—Na: serum sodium concentration
U—Na: urinary sodium concentration.

Data analysis

Patients demographic data, vital signs, urine flow, Ccr, and FE_{Na} before PGE_1 or control infusion, and the volume of lactated Ringer's solution infused during the study period were compared among the four subgroups by analysis of variance. Bonferroni's correction was applied as appropriate. Plasma ADH concentrations were compared between the EPI and GA groups using Student's t test. Each haemodynamic variable during the infusion period was compared with its baseline value using ANOVA. Changes of minute urinary flow, Ccr and FE_{Na} between EPI-PG and EPI-C subgroups, between GA-PG and GA-C subgroups, and between EPI-PG and GA-PG subgroups were carried out using ANOVA. A P value less than 0.05 was considered to indicate statistical significance.

Results

Two patients in the EPI-PG and three patients in the GA-C subgroups were excluded from the study because of elevated serum creatinine concentration before surgery. One patient in the EPI-PG and two patients in the EPI-C and GA-PG subgroups were excluded because their urinary flow before the infusion period was <0.5 $ml \cdot kg^{-1} \cdot hr^{-1}$. Analyses were carried out using the remaining 86 patients' data.

There were no differences in the demographic data or in the baseline values of PaO_2, $PaCO_2$, mean blood pressure (MAP), heart rate (HR), urine flow, Ccr, and FE_{Na} before the infusion period among the four subgroups (Table I, II). The volume of lactated Ringer's solution infused during the study was similar between the GA-PG and GA-C subgroups, and between the EPI-PG and EPI-C subgroups (Table I). Mean plasma ADH concentration (±SE) in the GA group (12.5 ± 2.6 $U \cdot L^{-1}$) was higher than in the EPI group (2.3 ± 0.8 $U \cdot L^{-1}$), $P < 0.001$.

In EPI-PG subgroup, PGE_1 infusion did not produce any changes in urinary flow, Ccr, and FE_{Na}, but in the EPI-C subgroup, there was a decrease in urinary flow (Figure 1). On the contrary, in the GA-PG subgroup, there were increases in urinary flow, Ccr and FE_{Na} ($P < 0.01$) (Figure 1).

Percent changes in urinary flow, Ccr, FE_{Na} in GA-PG subgroup were greater than those in GA-C subgroup ($P < 0.01$). Urinary flow increased by 114 ± 46%, Ccr by 74 ± 26% and FE_{Na} by 54 ± 23% in GA-PG subgroup (Figure 2).

Discussion

The principal findings of the present study were that lum-

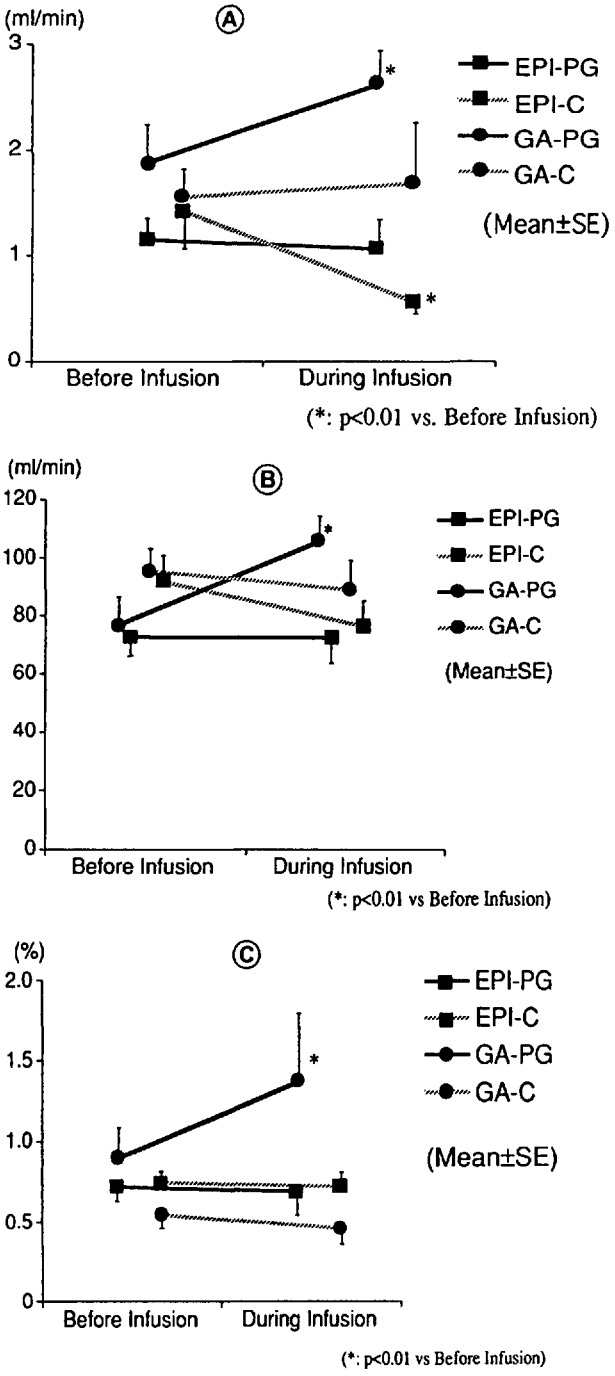

FIGURE 1 (A) Urinary flow, (B) Ccr, and (C) FE_{Na}. In the EPI group, urinary flow did not change during PGE_1 infusion, but decreased during control infusion: Ccr and FE_{Na} did not change. In the GA group, urinary flow, Ccr, and FE_{Na} increased during PGE_1 infusion but not in the control subgroup.

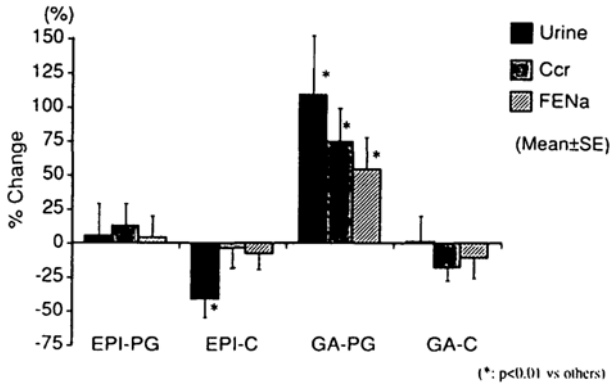

FIGURE 2 The percent changes in urinary flow, Ccr, and FE_{Na} in the four subgroups. Zero % indicates Before-infusion value. PGE_1 infusion increased urinary flow, Ccr and FE_{Na} significantly in GA group compared with those in the EPI group, respectively.

bar epidural anaesthesia prevented increases in urinary flow, Ccr and FE_{Na} induced by PGE_1 infusion. Haemodynamic changes in the EPI-PG subgroup during PGE_1 infusion were comparable with those in the GA-PG subgroup except for the absence of an increase in heart rate, which may indicate thoracic sympathetic block induced by lumbar epidural anaesthesia.

In the presence of surgical stress, cathecolamine and/or angiotensin-induced renovascular contraction[7] PGE_1 has been shown to dilate the renal artery. In animal studies,[8,19-21] PGE_1 increased renal blood flow but did not affect Ccr and this was considered to indicate that PGE_1 dilates not only afferent but also efferent arterioles in animals[8] so that the filtration ratio is not increased. The effect of PGE_1 on renal afferent and efferent arterioles in humans has not been reported. However, in the present study, PGE_1 increased Ccr in the GA-PG subgroup. Thus, it is possible that PGE_1 may affect the arterioles differently and result in an increase of Ccr in humans.

Urinary sodium excretion is enhanced by PGE_1 in the presence of increased plasma ADH concentrations.[10-13] Bonnet *et al.*[14] reported that ADH concentration during surgery under epidural anaesthesia was less than with general anaesthesia, and this is similar to the present results. Intravascular volume and surgical procedures may affect diuretic status, but in this study the fluid infused and the surgical procedures were similar in the PG and control subgroups of both the GA and the EPI groups. Therefore, the difference of PGE_1-induced effect on FE_{Na} in patients with or without lumbar epidural anaesthesia is likely to be due to the difference of plasma ADH concentration.[22,23] In addition, the decreased perfusion pressure in the EPI-PG subgroup might have contributed to the absence of an increase in FE_{Na}.[24,*]

The differences in surgical procedures and hydration status between the patients given general anaesthesia with

**Schneider E, McLane-Vega L, Hanson R, Childers J, Gleason S.* Effect of chronic bilateral renal denervation on daily sodium excretion in the conscious dog. Fed Proc 1978; 37: 645.

lumbar epidural anaesthesia and those given general anaesthesia alone may have affected the results.[25] However, the PGE_1-induced diuretic effect was compared with each sham control, so that comparisons of percent changes of urinary flow, Ccr, and FE_{Na} between the EPI and GA groups, or between the PG and C subgroups within EPI or GA group, respectively, did not affect the statistical analysis. In oliguric subjects or in subjects in whom residual urine volume is considerable, Ccr may not be a reliable test of glomerular function,[17,26] so that subjects who were oliguric before PGE_1 infusion were excluded from the study and the residual urine was expelled by the surgeons.

Although PGE_1 is unlikely to be used to produce deliberate hypotension in patients receiving general anaesthesia combined with epidural anaesthesia, this study suggests a beneficial effect by maintaining urinary flow with the PGE_1 infusion even though it is accompanied by mild hypotension.

In conclusion, PGE_1 produced a diuretic effect in patients receiving general anaesthesia during surgery, but this was not seen in patients who received lumbar epidural anaesthesia in addition. The results suggest that the mechanism of PGE_1-induced diuretic effect in humans includes increases in Ccr and FE_{Na}.

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