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Epidural Analgesia Combined with a Small-Dose of Fentanyl Attenuates the Endocrine Responses and Renal Tubular Damage during Thoracotomy

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Abstract

The purpose of this study is to investigate the hypothesis that epidural analgesia combined with fentanyl suppresses endocrine responses and prevents renal impairment during thoracotomy. Thirty patients undergoing elective lung lobectomy via thoracotomy were randomly divided into three groups according to the anesthetic method. The patients of group GA received only general anesthesia. Those in group CGE received general anesthesia and epidural analgesia with 1% mepivacaine. Those in group F received general anesthesia, epidural analgesia with 1% mepivacaine, and fentanyl given both intravenously and to the epidural space. Plasma cortisol and aldosterone were measured as indicators of the endocrine response. Urinary output of N-acetyl-beta-D-glucosaminidase (NAG) was also measured as an indicator of renal tubular damage. In group F, NAG and cortisol releases were suppressed. NAG increased by 191% and by 119%, and cortisol increased by 247% and by 167% in group GA and CGE, respectively ($p<0.05$). In group F, the aldosterone release was attenuated down to 48% over the preoperative values, while it increased markedly by 358% and by 264%, in group GA and CGE, respectively. These results suggest that fentanyl in addition to epidural analgesia attenuates the endocrine responses and the renal tubular damage during thoracotomy.

Key words; epidural analgesia, fentanyl, endocrine responses, renal tubular damage, thoracotomy

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Introduction

Surgical stress produces a variety of endocrine responses, including sympathetic hyperactivity and cytokine release[1,2]. Elevated plasma levels of cortisol and aldosterone have been reported to be associated with renal impairment during thoracotomy under general anesthesia with volatile anesthetics[3]. The intravenous administration of high-dose of fentanyl can prevent those responses and thus can preserve the renal function. Epidural analgesia (EA), meanwhile, blocks nociceptive stimuli from the surgical site and attenuates significant increases in adrenalin, noradrenalin and systemic vascular resistance in aortocoronary bypass surgery[4]. We hypothesized that EA combined with a small-dose of fentanyl can thus suppress excessive endocrine responses, thereby preventing renal impairment. Renal impairment following thoracotomy should be an issue in the strict management of fluid balance and it significantly increases both mortality and morbidity[5]. Our objective in this study is to evaluate the effects of EA in the presence and absence of a small-dose of fentanyl on the endocrine response and renal impairment during thoracotomy.

The plasma concentrations of cortisol and aldoster-

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one were measured as indicators of the endocrine response representing a stress reaction and renal blood flow, respectively. The urinary output of N-acetyl-beta-D-glucosaminidase (NAG) was measured as a sensitive indicator for renal tubular damage, which is speculated to occur at the beginning of acute renal impairment.

Materials and methods

This study was conducted at Mitsui Memorial Hospital. The study design was approved by the Ethics Committee of the hospital. Thirty patients without any existing renal or endocrine diseases rated as American Society of Anesthesiologist physical status of 1 or 2 were scheduled to undergo an elective lung lobectomy via a thoracotomy. All patients received a comprehensive and detailed explanation of the study protocol and informed consent was obtained from all individuals enrolled in this study.

The patients were randomly divided into three groups of 10 patients each according to the anesthetic method using the table of random numbers. The patients of group GA received general anesthesia (GA) only, those of group CGE received GA and EA with 1% mepivacaine, and those of group F received GA, EA with 1% mepivacaine, and fentanyl given both intravenously and to the epidural space.

The subjects received an intramuscular injection of atropine 0.5mg and hydroxydine 25mg 60min before the induction of anesthesia. In the operating room, a venous cannula was inserted via the antecubital vein. Basic monitoring was performed including an automatic manometer of blood pressure, electrocardiogram, pulse oximetry, capnography, and anesthetic gas monitor. An arterial cannula was inserted in the radial artery for blood pressure monitoring and sampling. Before the induction of general anesthesia, the epidural catheter was inserted 5cm into the cephalad direction via Th4-5 for all patients. After a 2-min observation period from the administration of 1% mepivacaine 2ml as a test dose, 7ml of 1% mepivacaine for the group CGE and 4ml of 1% mepivacaine with 0.2mg fentanyl for group F were administered through the epidural catheter. In addition, 4ml of 1% mepivacaine was administered at 45-min intervals in these two groups.

GA was induced with thiamylal $6mg \cdot kg^{-1}$ for the group GA and CGE, and $4mg \cdot kg^{-1}$ in addition to fentanyl 0.1mg for the group F intravenously. Intubation with a double lumen tube (BronchoCath Tube, Tyco Healthcare Inc., Ireland) was facilitated by vecuronium $0.12mg \cdot kg^{-1}$. General anesthesia was maintained with isoflurane 1.5～2.0% for group GA and 0.5～1.0% for the other groups, and nitrous oxide 0～50% in oxygen 50～100%. After the experimental period, 1% mepivacaine was administered epidurally at 45-min intervals to all patients of three groups.

Blood samples were drawn through the arterial line and collected in a test tube containing EDTA as a chelator in order to measure the plasma cortisol and aldosterone concentrations. Blood samples were drawn before epidural injection of the test dose (preoperative sample), and one hour after skin incision (intraoperative sample). After centrifugation at 4℃, the plasma and serum were stored at −20℃. The cortisol and aldosterone concentrations were determined with solid-phase radioimmunoassay kits.

Urine samples were obtained at the time intervals described above for a stress hormone assay in order to measure the urinary output of NAG. Urine specimens were collected in a test tube from the Foley catheter and were subsequently stored at −20℃. Urinary NAG concentration was determined with a NAG kit and expressed as the urinary output (U) per 1g of creatinine output.

The results are expressed as the mean±standard deviation for each group. Differences between the preoperative and intraoperative values within the same group were assessed by Student's paired t test. Differences in the means among the three groups were assessed with the Bonferroni/Dunn test in addition to an analysis of variance. P values of less than 0.05 were considered to be significant.

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Table 1 Clinical data for the three groups

group	GA	CGE	F
age (y.o.)	58.8±16.2	57.4±18.6	61.9±9.3
gender (male/female)	7/3	7/3	8/2
average concentration of isoflurane (%)	1.7±0.5*	0.9±0.4	0.9±0.2
urinary output (ml/kg/hr)	0.95±0.45	1.10±0.30	2.01±0.67*
crystalloid infusion (ml/kg/hr)	9.1±3.1	9.4±3.3	9.3±2.5
blood loss (ml/3hr)	231.8±138.8	200.2±78.3	289±112.1

Data are mean±SD. *: $p<0.01$ compared with other two groups.

Results

Table 1 summarizes the clinical data for the three study groups. The urine volumes in group F were about twofold greater than those in the other groups, although the crystalloid infusion rates were not significantly different. The subjects in group GA inhaled a significantly higher average concentration of isoflurane. The operation times were not significantly different among the groups (The data are not shown.). There were no significant differences in mean arterial pressure among the groups during the study periods, as **Table 2** shows the hemodynamic data for the three groups. At one hour after skin incision, however, the heart rate in group CGE was significantly less than that in group GA ($p<0.01$). Epidural analgesia ranged about Th1-Th9 evaluated by cold sensation.

The cortisol levels increased significantly during thoracotomy in group GA and in group CGE ($p<0.01$), from 8.2±3.1 and 9.9±4.8 to 24.5±7.8 and 23.6±9.0 $\mu g \cdot dl^{-1}$, respectively. On the other hand, they decreased significantly from 7.9±3.1 to 5.9±3.0 $\mu g \cdot dl^{-1}$ in group F ($p<0.01$). Furthermore, the cortisol levels of group F were significantly lower than those of the other groups at 1 hr after skin incision ($p<0.01$). As shown in **Fig. 1** the change rate in the cortisol levels in group CGE was lower than in group GA, but the difference was not significant.

The plasma levels of aldosterone significantly increased more than threefold during thoracoromy in group GA and in group CGE ($p<0.01$), from 35.1±22.4 and 40.6±24.1 to 119.2±68.1 and 123.0±82.7 $pg \cdot ml^{-1}$, respectively. In group F, those increased less than twofold ($p=0.025$), from 32.3±12.2 to 48.3±26.5 $pg \cdot ml^{-1}$. In addition, the aldosterone levels of group F were significantly lower than those of the other groups at 1 hr after the skin incision ($p<0.05$). **Fig. 2** shows the change rate of the aldosterone level.

Table 2 Hemodynamic data for the three groups

group		pre-ope	ope-1hr
GA	MAP (mmHg)	81±11	83±13
	HR	75±10	80±10
CGE	MAP (mmHg)	78±9	77±8
	HR	69±9	65±8*
F	MAP (mmHg)	78±8	85±11
	HR	65±9	71±10

Data are mean±SD.
*: $p<0.05$ compared with control group.
HR = heart rate.
MAP = mean arterial pressure.
pre-ope = preoperative period, ope-1hr = 1hr after skin incision

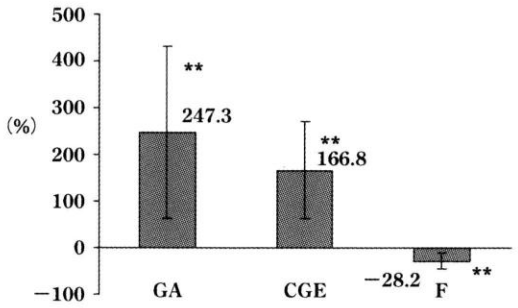

Figure 1 The change rate in the cortisol level during a thoracotomy.
**: $p<0.01$ compared with preoperative period
GA = group GA, CGE = group CGE, F = group F

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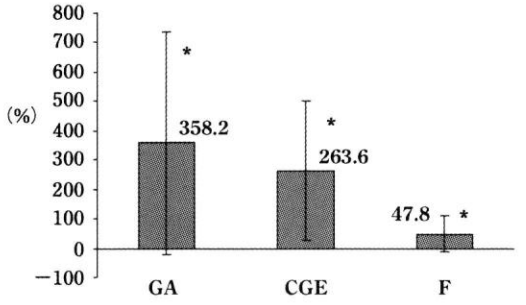

Figure 2 The change rate in the aldosterone level during a thoracotomy.
*: $p<0.05$ compared with preoperative period
GA=group GA CGE=group CGE F=group F

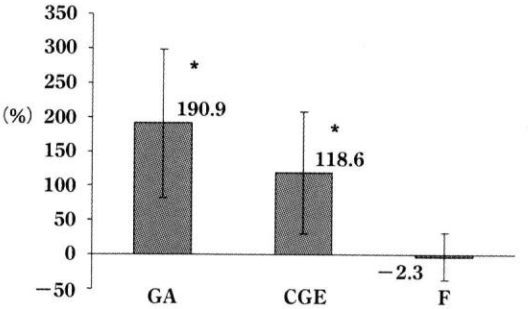

Figure 3 The change rate in the urinary NAG output during a thoracotomy.
*: $p<0.05$ compared with the preoperative period
GA=group GA CGE=group CGE F=group F

Urinary NAG output increased during thoracoromy in group GA and in group CGE, from 4.6±2.4 and 6.5±2.6 to 12.0±4.9 and 15.3±11.0 U·1g creatinine^{-1} ($p<0.05$), respectively. In group F, the urinary NAG output did not increase significantly from 6.6±4.0 to 6.0±3.2 U·1g creatinine^{-1}. The NAG output values of group F were significantly lower than those of the other groups at 1 hr after skin incision ($p<0.05$). **Fig. 3** shows the change rate of the urinary NAG output which was similar to that of the cortisol level shown in **Fig. 1**.

Discussion

In this study, EA combined with a small-dose of fentanyl was capable of attenuating the stress responses as indicated by the changes in the serum cortisol and aldosterone concentrations during thoracotomy, while EA with local anesthetics demonstrated such properties incompletely. The change in the urinary NAG output caused by thoracotomy was suppressed with a small-dose of fentanyl in addition to EA, but not significantly with EA only. Furthermore, the urine output volume of group F was significantly greater than of the volumes in the other groups.

We administered fentanyl intravenously and epidurally to attenuate nociceptive stimuli of intubation and surgical procedure, respectively. Epidural fentanyl administered as a bolus injection is reported to act predominantly at spinal sites[6], and it in combination with local anesthetics is commonly used for the postoperative pain control[7]. We used epidural fentanyl with local anesthetics as a bolus injection during surgery based on the hypothesis that their effect in reducing the amount of both the local anesthetics administered epidurally and the volatile anesthetics inhaled in order to attenuate cardiovascular change. Although the larger amount of local anesthetics in group CGE may significantly suppress the endocrine response, cardiovascular deterioration occurring under such conditions remains an issue. In addition, it may also worsen the renal circulation. We therefore tried to determine the optimal dose of local anesthetics in order to prevent cardiovascular deterioration.

In this study, EA combined with a small-dose of fentanyl suppressed cortisol release induced by surgical stress, while epidural analgesia with local anesthetics was not found to be significantly effective. The issue is whether fentanyl acts only at the spinal cord or possibly also at some other sites as well. The intravenous administration of high-dose of fentanyl has also been reported to suppress an excessive endocrine response[8,9]. Humoral substances such as cytokines from the site of injury directly act on the hypothalamus and other organs. Cortisol release during surgery is also altered as a result of cytokines that reach the hypothalamic nuclei[10,11]. The effect of fentanyl and other narcotic drugs on cytokine release remains controversial. Alfentanil has been reported to attenuate interleukin-6 release during abdominal surgery[12], while fentanyl has been demonstrated to suppress the increase of TNF-alfa and interleukin-1

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by global cephalic ischemia and reperfusion in rat[13]. However, data from some clinical studies suggest that fentanyl and sufentanil do not influence cytokine release[14~16]. Further study is needed to demonstrate the mechanism that fentanyl suppress cortisol release.

Surgical procedures cause changes in the fluid metabolism and induce renal vasoconstriction with sympathetic hyperactivity. In addition, all volatile anesthetics and EA tend to decrease renal blood flow[17]. The renin-angiotensin system that regulates aldosterone release is influenced by glomerular perfusion and it is also activated by surgical stimuli and anesthesia. The administration of fentanyl blocks nociceptive stimuli and reduces the concentration of inhaled anesthetics and local anesthetics for EA. As a result, fentanyl could prevent renal circulatory deterioration resulting from surgical stress and anesthetics. This finding is in agreement with the urine output volume of group F, which is greater than those volumes observed in other groups. Therefore the change in the aldosterone release was attenuated by the administration of fentanyl during thoracotomy, while it is slightly affected by EA with local anesthetics. EA also blocks nociceptive stimuli and reduces the concentration of inhaled anesthetics as much as fentanyl, but it also simultaneously decreases the renal blood flow. As a result, the effects of EA would be offset. As **Fig. 2** shows, the large standard deviation observed in the change rate in group GA may thus be due to a small sample size, and that various degrees of surgical stimulation are not blocked and therefore such stimulation may directly influence the aldesterone release. As a result, the standard deviations of group GA may be larger than those of the other groups.

In this study, damage to renal tubular cells was evaluated because renal tubules are anatomically susceptible to both ischemic and hypoxic injury and they can therefore predict renal impairment. The urinary output of NAG, which is a lysosomal enzyme in renal tubular cells, is a sensitive indicator of tubular damage[18]. Indeed, the urinary output of NAG has been reported to be an indicator of renal tubular damage during cardiac surgery[19,20], and as one of urinary enzymes for predicting patient prognosis in acute renal failure[21]. In this study, NAG significantly increased during surgery in group GA and in group CGE, but not in group F. The change in the renal blood flow may thus be able to influence the urinary excretion of NAG. The administration of fentanyl could preserve the renal blood flow as described previously. On the other hand, humoral substances may affect the urine NAG output. Urinary tripsin inhibitor has been reported to prevent the elevation of interleukin 8, polymorphonuclear leukocyte elastase, and urinary NAG following major surgery[22]. As a result, the increase in urinary NAG during surgery may be mediated by humoral agents, which would thus be blocked with fentanyl.

In conclusion, this study suggests that a small-dose of fentanyl, in addition to EA, attenuates the endocrine responses, thus preventing renal tubular damage during thoracotomy. This anesthetic method may thus be beneficial for the postoperative management of the fluid balance and the control of an adverse reaction by surgical stress.

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