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Epidural block during general anesthesia attenuates urinary trypsin inhibitor excretion in lower abdominal surgery

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Abstract

Purpose. The aim of this study was to elucidate whether urinary trypsin inhibitor excretion differs between general anesthesia (GA) and epidural block during general anesthesia (EPI) in lower abdominal surgery.

Methods. Sixteen women undergoing abdominal total hysterectomy were assigned to the GA and EPI groups. The GA group received propofol induction and maintenance with isoflurane, nitrous oxide, and vecuronium. The EPI group received epidural block, followed by propofol induction and maintenance with isoflurane and nitrous oxide. The levels of adrenocorticotropic hormone and cortisol during anesthesia and on postoperative days 1, 2, and 3, and the levels of urinary trypsin inhibitor in 12-h urine from the day of surgery to postoperative day 3, were measured.

Results. As compared with the EPI group, the GA group had a higher level of adrenocorticotropic hormone at the completion of anesthesia, higher levels of cortisol at the completion of anesthesia and postoperative day 2, and higher excretion of urinary trypsin inhibitor on the day of surgery and postoperative days 1 and 2.

Conclusion. The present results suggest that excretion of urinary trypsin inhibitor into the urine under epidural block during general anesthesia is lower than that under general anesthesia alone in lower abdominal surgery. This is probably due to the difference in endocrine response to surgery between the two types of anesthesia.

Key words: Endocrine response, Epidural anesthesia, General anesthesia, Lower abdominal surgery, Urinary trypsin inhibitor.

Introduction

Urinary trypsin inhibitor (UTI) is an acid-stable glycoprotein and a physiological and multipotential protease inhibitor [1,2], which inhibits not only various serine proteases such as trypsin, α-chymotrypsin, leukocyte elastase, plasmin, and cathepsin G, but also hyaluronidase and collagenase [3,4], and which is rapidly excreted into the urine, probably from the blood via the kidney [5]. However, its biological function has not been completely determined. The UTI in blood seems to be converted from inter-α-trypsin inhibitor synthesized in the liver [6–9], and its production is accelerated after administration of steroids [1,10–12]. Therefore, UTI excretion into the urine increases in inflammatory diseases, pregnancy, and postsurgical states [1].

It is known that epidural block up to around the 4th thoracic dermatome level completely inhibits acute endocrine responses to surgery in lower abdominal surgery, for instance, increases of adrenocorticotropic hormone (ACTH) and cortisol (CS) at the early phase [13,14]. The aim of this study was to elucidate whether UTI excretion into the urine differs between general and epidural anesthesia in this class of surgery.

Patients and methods

After approval of the Institutional Committee, 16 adult women classified as ASA 1 who provided informed consent and received abdominal total hysterectomy for benign diseases were assigned randomly into two groups of 8 patients each: general anesthesia alone (GA) and epidural block during general anesthesia (EPI). All patients had normal values in the preoperative screening examinations and were premedicated with 0.01 mg·kg^{-1} atropine and 1 mg butorphanol i.m. 1 h before entering the operating room.

In the GA group, the anesthesia was induced with 1.5 mg·kg^{-1} propofol, 1.5% isoflurane, and 33% O_2/N_2O, and tracheal intubation was facilitated with vecuronium. The anesthesia was maintained with 1.5–2.0% isoflurane and 33% O_2/N_2O. At completion of the sur-

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gery, a 50 mg diclofenac suppository was inserted. For postoperative pain relief, the same suppository was inserted appropriately when the patient complained of pain and requested analgesics. In the EPI group, an epidural catheter was inserted cephalad via the L1-2 interspace, and 12 ml of 2% mepivacaine was injected. Fifteen minutes later, the extent of hypesthesia was tested using an alcohol swab. Subsequently, 1.5 mg·kg^{-1} propofol was administered, and 0.5% isoflurane with 33% O_2/N_2O was inhaled with manual assisted ventilation using a face mask. During the surgery, 6–8 ml of 2% mepivacaine was injected epidurally at a 45-min interval. After the surgery, 4 ml·h^{-1} of 0.25% bupivacaine was continuously injected epidurally for pain relief until 48 h later. Thereafter, the epidural catheter was removed and a 50 mg diclofenac suppository was inserted as needed. In all patients, an urinary catheter was inserted at 1200 hours and the surgery was performed at 1300–1600 hours.

Total urine over 12 h at 1200–2400 hours on the day of surgery (0–12 h), 0–1200 hours (12–24 h) and 1200–2400 hours (24–36 h) on postoperative day (POD) 1, 0–1200 hours (36–48 h) and 1200–2400 hours (48–60 h) on POD 2, and 0–1200 hours (60–72 h) and 1200–2400 hours (72–84 h) on POD 3 were collected. Venous blood was collected before induction of general or epidural anesthesia, at the time of completion of anesthesia, and in the morning on POD 1, 2, and 3. UTI, creatinine, and *N*-acetyl-β-D-glucosaminidase (NAG) concentrations of the total 12 h urine were measured. Plasma levels of ACTH and serum levels of CS, C-reactive protein (CRP), blood urea nitrogen (BUN), and creatinine were measured. UTI was assayed by radioimmunoassay using an assay system from Sumitomo Kinzoku Bioscience, Tokyo, Japan.

Data are presented as means ± SD. Demographic data, including age, height, weight, fluid transfusion volume, estimated blood loss, and time of surgery, were compared by the unpaired *t*-test. For comparison of other data between the groups, repeated-measure analysis of variance was selected. When statistical significance existed, the unpaired *t*-test was performed at each measurement time. For comparison within the group, repeated-measure one-way analysis of variance, followed by the Fisher PLSD, was performed in which the induction value or 0–12 h value was compared with other values. $P < 0.05$ was considered significant.

Results

Demographic data and clinical course

There were no statistically significant differences between the groups in age, height, weight (Table 1). The fluid transfusion volume during anesthesia and its total volume on the day of surgery in the EPI group showed significantly higher values ($P < 0.05$). There were no significant differences with regard to estimated blood loss and duration of surgery between the GA and EPI groups. The upper anesthetized thoracic dermatome level in the EPI group was 5.3 ± 1.3.

Table 1. Demographic data

Patient characteristic	GA group	EPI group
n	8	8
Age (yr)	44 ± 4	43 ± 6
Height (cm)	156 ± 6	154 ± 4
Weight (kg)	56 ± 7	56 ± 5
Fluid transfusion (ml)		
During anesthesia	1023 ± 115	1470 ± 510*
Total on day of surgery	3813 ± 259	4438 ± 496*
Estimated blood loss (ml)	150 ± 84	169 ± 169
Time of surgery (min)	63 ± 14	64 ± 15

GA, General anesthesia; EPI, epidural block during general anesthesia. * $P < 0.05$ vs. GA group

All patients received anesthesia and surgery with no clinical problems and showed an uneventful course after surgery. Postoperative laboratory examination, including liver function, was performed on POD 1 and 7, although no patients had liver dysfunction.

Urinary volume, creatinine clearance, and serum BUN and creatinine levels

The time course of urinary volume did not differ significantly between the GA and EPI groups. In the GA group, urinary volume increased significantly at 12–24 h, 24–36 h, and 60–72 h ($P < 0.05$). In the EPI group, urinary volume increased significantly at 24–36 h ($P < 0.05$).

The time course of creatinine clearance did not differ significantly between the GA and EPI groups. In both groups, creatinine clearance values were normal and did not change significantly.

The time course of serum BUN and creatinine levels did not differ significantly between the GA and EPI groups. In both groups, BUN and creatinine values were normal and did not change significantly.

Circulation during anesthesia

Systolic blood pressure in the GA group was significantly higher than in the EPI group after the beginning of the surgery ($P < 0.05$) (Fig. 1). In the GA group, systolic blood pressure decreased significantly after the induction of anesthesia ($P < 0.05$) but resumed during surgery and at the completion of anesthesia. In the EPI group, systolic blood pressure decreased significantly after the induction of anesthesia and maintained

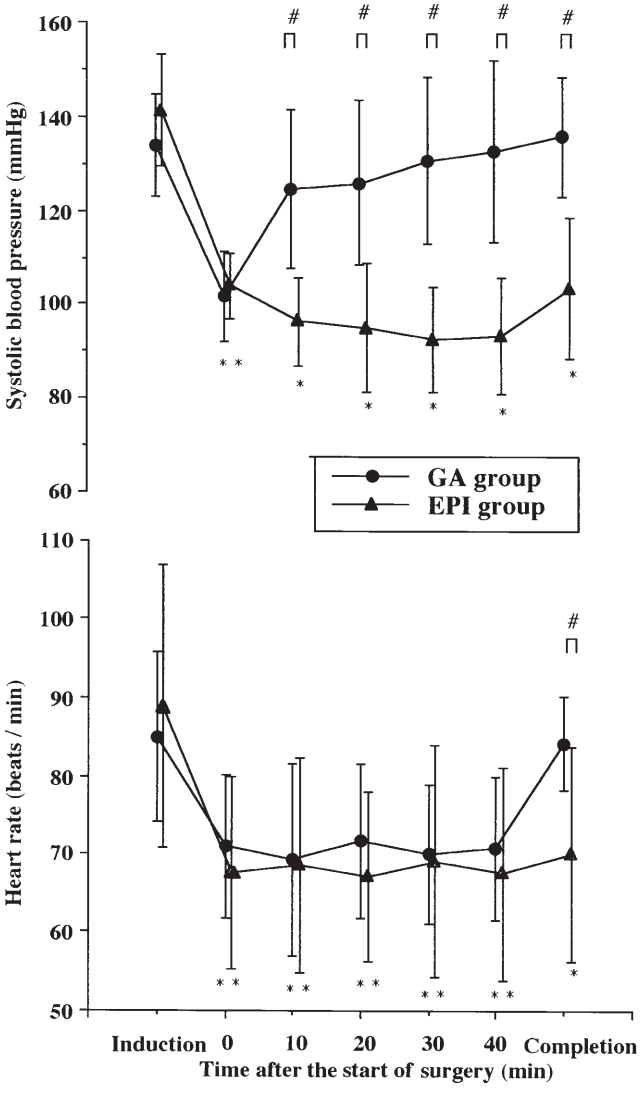

Fig. 1. Time course of systolic blood pressure and heart rate. *GA*, General anesthesia; *EPI*, epidural block during general anesthesia. *$P < 0.05$ vs. induction value. #$P < 0.05$ between groups

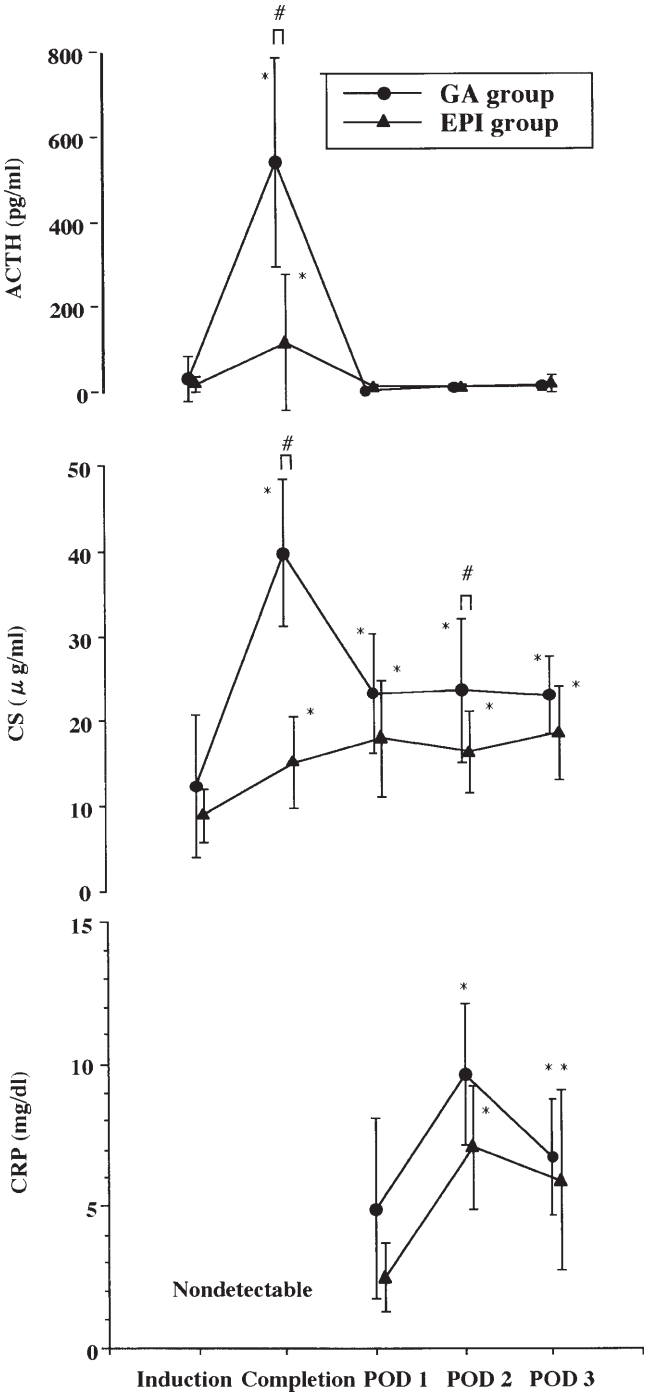

Fig. 2. Time course of plasma adrenocorticotropic hormone (*ACTH*) level and serum cortisol (*CS*) and C-reactive protein (*CRP*) levels. *GA*, General anesthesia; *EPI*, epidural block during general anesthesia; *POD*, postoperative day. *$P < 0.05$ vs. induction value or POD 1 value. #$P < 0.05$ between groups

decreased values until the completion of anesthesia ($P < 0.05$).

Heart rate in the GA group was significantly higher than in the EPI group at the completion of anesthesia ($P < 0.05$). In the GA group, heart rate decreased significantly after the induction of anesthesia and during surgery ($P < 0.05$), but resumed at the completion of anesthesia. In the EPI group, heart rate decreased significantly after the induction of anesthesia and maintained decreased values until the completion of anesthesia ($P < 0.05$).

Plasma ACTH level, and serum CS and CPR levels

The plasma ACTH level in the GA group was significantly higher than in the EPI group at the completion of anesthesia ($P < 0.05$) (Fig. 2). At this time, the ACTH levels in both groups increased significantly ($P < 0.05$).

The serum CS levels in the GA group were significantly higher than in the EPI group at the completion of

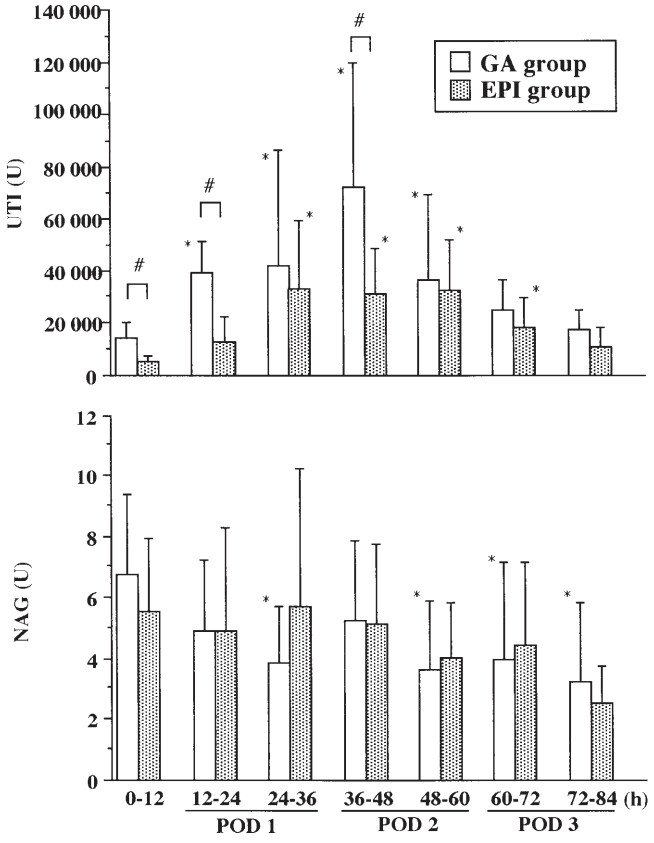

Fig. 3. Time course of total excretion of urinary trypsin inhibitor (*UTI*) and *N*-acetyl-β-D-glucosaminidase (*NAG*) in 12-h urine. *GA*, General anesthesia; *EPI*, epidural block during general anesthesia; *POD*, postoperative day. *$P < 0.05$ vs. 0–12 h value. #$P < 0.05$ between groups

anesthesia and on POD 2 ($P < 0.05$). The CS levels in both groups increased significantly until POD 3 ($P < 0.05$).

Serum CRP at induction and at the completion of anesthesia was nondetectable in all patients. From POD 1 to 3, there was no significant difference between the GA and EPI groups. CRP levels on POD 2 and 3 in both groups increased significantly as compared with those on POD 1 ($P < 0.05$).

Total UTI and NAG excretion in 12-h urine

Total UTI excretion in the GA group was significantly higher than in the EPI group at 0–12 h, 12–24 h, and 36–48 h ($P < 0.05$) (Fig. 3). In the GA group, UTI excretion increased significantly until 48–60 h ($P < 0.05$). In the EPI group, UTI excretion increased significantly from 24–36 h to 60–72 h ($P < 0.05$).

Total NAG excretion did not differ significantly between the GA and EPI groups. NAG excretion in the GA group decreased significantly at 24–36 h, 48–60 h, 60–72 h, and 72–84 h ($P < 0.05$), but did not change significantly in the EPI group.

Discussion

Since UTI is quickly excreted into the urine [5], urinary excretion of UTI has been regarded as the index of systemic UTI concentration, in which the revised value ($U \cdot mg^{-1}$) calculated by dividing urinary UTI concentration ($U \cdot ml^{-1}$) by urinary creatinine concentration ($mg \cdot dl^{-1}$) is used, particularly when casual or short-time urine is sampled [15,16]. However, whether this revised value accurately reflects systemic UTI concentration has not been demonstrated. Thus, we compared total UTI excretion in 12-h urine between the groups in this study, in order to estimate the difference in systemic UTI concentration. Furthermore, the results of urinary volume, creatinine clearance, and serum BUN and creatinine levels in this study showed no differences between the groups, which may support this comparison.

UTI excretion into urine exhibits a circadian rhythm as it increases in the morning and decreases in the evening in the same way as the CS rhythm [10], and urinary excretion and serum level of UTI increase after administration of CS [11,12]. Furthermore, urinary UTI excretion correlates with serum CRP level after surgery [15,17], in which the peak excretion is around POD 3 after major surgery [15]. Although UTI is converted from inter-α-trypsin inhibitor [6–9], one report [12] demonstrated that UTI itself is also produced in the liver. Whether inter-α-trypsin inhibitor correlates with serum CRP level remains unknown. Inflammatory cytokines such as interleukin-6 cause delayed endocrine responses to surgery as well as increasing serum CRP level produced in the liver several hours after the start of surgery [14,18]. Although whether this cytokine affects UTI production in the liver is unclear, this production, based on these reports, may be essentially regulated by inflammatory cytokines. Under these conditions, the extent of increased CS may additionally accelerate UTI production in the liver.

In the lower part of the abdomen, early endocrine responses to surgery, until several hours after the start of surgery, indicate the difference between general and epidural anesthesia, in which increased CS is completely inhibited by epidural anesthesia extending around the 4th thoracic dermatome level [13,14]. This effect is due to suppression of the neural pathway of the surgical insult. After this period, delayed endocrine responses by inflammatory cytokines are added to this early response [14,18]. The EPI group in this study showed almost no change in ACTH and a gradual increase in CS, whereas the GA group showed significant increases in ACTH and CS. Thus, these results are consistent with

these reports. Since postsurgical elevation of the serum CRP level in both groups was the same, inflammatory cytokines produced from the surgical wound might be equal, suggesting similar surgical insults, resulting in similar cytokine-induced UTI production. Until several hours after the start of surgery, however, UTI excretion into the urine is probably caused by only the extent of increased CS level by early endocrine responses. After this period, UTI excretion is probably caused by both CS-induced UTI production and subsequent cytokine-induced UTI production. The results of total UTI excretion in this study may be consistent with these implications, suggesting that UTI excretion under epidural block during general anesthesia is lower than that under general anesthesia alone, due to the difference in endocrine responses between these types of anesthesia.

Although the present results document a new finding, whether clinical significance exists remains unclear. To consider this implication, the physiologic role of UTI and its purified drug of ulinastatin (Mochida Pharmaceutical Co., Tokyo, Japan) used clinically in Japan [2] should be discussed. Ulinastatin has been demonstrated to be effective for acute pancreatitis [3] and circulatory collapse [19,20]. One unit of ulinastatin inhibits 50% of the activity of 2 μg of trypsin. In addition to these actions, animal experiments have revealed that ulinastatin exerts protective effects on ischemic acute renal failure [21] and cisplatin-induced renal injury [22]. Furthermore, many clinical and experimental studies [23–27] have suggested that this drug has beneficial effects on tubular injury from several episodes of acute renal failure. Yamasaki et al. [28] reported that ulinastatin lessens the release of NAG and a marker enzyme of lysosomes from the renal cells, and this effect is markedly potentiated after cisplatin treatment. Although its mechanism in the kidney is not fully understood, amelioration of lysosomal fragility may be one of the mechanisms by which ulinastatin protects the proximal renal tubule against cellular injury [28]. In this study, we measured urinary NAG excretion and other kidney-related values, but postsurgical renal function was completely preserved in all patients. These results seemed to be appropriate, because the patients examined were classified as ASA 1 and received moderate surgical insults with minimal blood loss and duration of surgery. One report [16] examined UTI excretion in patients with liver cirrhosis after major surgery, and showed a small increase in UTI excretion with augmentation of NAG excretion, suggesting postoperative renal dysfunction. Replacement of ulinastatin in these patients during the perioperative period has been demonstrated to prevent this renal dysfunction [16]. Based on this discussion, replacement therapy with ulinastatin for patients with liver dysfunction may have beneficial effects in preserving postoperative renal function, particularly in combination with epidural block. Further studies to test this hypothesis are needed.

In conclusion, the present study demonstrates that UTI excretion into urine under epidural block during general anesthesia is significantly lower than that under general anesthesia alone in patients undergoing lower abdominal surgery. This finding may be attributed to the difference in endocrine responses to surgery between the two types of anesthesia.

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