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Epidural anesthesia during hysterectomy diminishes postoperative pain and urinary cortisol release

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Abstract
Purpose. To examine the hypothesis that epidural anesthesia throughout lower abdominal surgery would depress both postoperative pain and cortisol release.
Methods. Forty adult patients undergoing abdominal total hysterectomy were studied. The patients were randomly assigned to two groups. Group G received general anesthesia alone (sevoflurane 1.5%–2.5%); group E received a combination of epidural anesthesia (1.5% mepivacaine) with a light plane of general anesthesia (sevoflurane < 0.5%). Postoperative analgesia was obtained epidurally by patient-controlled analgesia. Postoperative pain at rest and during movement was assessed by a visual analogue scale (VAS) at 2, 24, and 48 h following surgery. The plasma concentration and urinary excretion of cortisol were measured during the perioperative period.
Results. VAS values were lower in group E than in group G during movement at 24 h (4.6 ± 0.5 *vs* 6.1 ± 0.4 cm). Urinary cortisol excretion on the first postoperative day was less in group E than in group G (192 ± 34 *vs* 480 ± 120 μg).
Conclusions. Epidural blockade prior to surgical stimuli and throughout lower abdominal surgery reduces the postoperative dynamic pain and stress response.

Key words: Cortisol, Epidural anesthesia, Hysterectomy, Preemptive analgesia, Visual analogue scale

Introduction

Noxious impulses from damaged tissue during surgery likely evoke long-lasting alterations in the central nervous system, i.e., the hyperexcitable state, considered as a clue element in the development of postoperative acute pain [1–3]. Recently, in both animal and clinical studies, with *N*-methyl-D-aspartate (NMDA) receptor blockade [4] and with local infiltration [5,6], respectively, preemptive analgesia has been shown to minimize subsequent pain by preventing this central sensitization. However, the efficacy of epidural anesthesia to obtain preemptive analgesia remains controversial [7–11]. In a previous study, we showed that the preincisional employment of epidural blockade during upper abdominal surgery reduced postoperative pain and the need for supplemental analgesics [12]. Similar results were obtained for patients undergoing lower abdominal surgery [11]. On the other hand, others were unable to show beneficial effects of epidural anesthesia on postoperative pain when administered before rather than after lower abdominal surgery [10], and also for major abdominal surgery [8]. The question could be raised whether the preincisional employment of epidural blockade to obtain preemptive analgesia indeed reduces the surgical stress throughout the perioperative period.

To assess the surgical stress and pain condition, the measurement of endocrine responses such as the release of catecholamines and cortisol has been commonly accepted [13,14]. Repeated entry of sensory signals from damaged tissue also plays a major role in eliciting such endocrine responses [15]. Indeed, epidural blockade to inhibit afferent pathways from the surgical area has produced no changes or fairly minor changes in plasma cortisol during and after surgery [16]. Katz and co-workers [11] recently demonstrated that preemptive single-shot epidural anesthesia depressed postoperative pain and the requirement for analgesics following lower abdominal surgery, although the plasma cortisol level and pain scores were not clearly different from those in nontreated patients. A question remains as to whether extending the preincisional epidural blockade throughout the surgery has more apparent benefits as a preemptive procedure. Therefore, we designed this randomized, blinded study to examine the hypothesis that epidural anesthesia prior to surgical incision and

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throughout lower abdominal surgery would depress both postoperative pain and cortisol release.

Methods and materials

After obtaining approval from our institutional ethics committee and informed consent from the patients, we studied 40 consecutive adult patients undergoing elective hysterectomy. The criteria for exclusion from the study were an ASA physical status rating of III or greater or the presence of coagulation or neurologic disorders. All patients received 150 mg of ranitidine orally at 9 P.M. on the day before the surgery and 50 mg hydroxyzine and 0.5 mg atropine intramuscularly 30 min before arriving in the operating room.

Study protocol

All patients had an epidural catheter (17-gauge, Flex Tip Plus, Arrow Japan, Tokyo, Japan) inserted at the L2-3 or L3-4 level before the induction of general anesthesia. The patients were then randomly allocated into two groups. Group E (n = 18) underwent continuous epidural anesthesia concomitant with a light plane of general anesthesia, and group G (n = 22) received only general anesthesia during the operation. The patients in group E received 15 ml of 1.5% mepivacaine epidurally, followed by continuous infusion of 1.5% mepivacaine at a rate of 7 to 10 ml·h^{-1}. Anesthesia was then induced with thiopental and succinylcholine to facilitate the placement of a laryngeal mask airway. Anesthesia was maintained with 67% nitrous oxide in oxygen with sevoflurane. The concentration of inspired sevoflurane was maintained at less than 0.5% throughout the operation. The patients breathed spontaneously during the operation. The patients in group G were given 15 ml of normal saline epidurally. After endotracheal intubation, anesthesia was induced with thiopental and succinylcholine and was maintained with nitrous oxide in oxygen with sevoflurane. The sevoflurane concentration was maintained between 1.5% and 2.5%, and muscle relaxation was achieved with intermittent injection of vecuronium bromide. No other analgesics, such as narcotics, were administered during the surgery. For 10 min before and after the surgical incision, systolic blood pressure (SBP) and heart rate (HR) were recorded every minute. These hemodynamic parameters were then monitored every 5 min throughout the surgery. End-tidal carbon dioxide pressure ($P_{ET}CO_2$) (Capnomac, Datex, Helsinki, Finland) was also monitored throughout the surgery. During the closing of the peritoneum, i.e., 15 to 20 min before the completion of the operation, buprenorphine (0.1 mg) in 8 to 12 ml of 0.25% bupivacaine was administered epidurally to all patients. After the patients had emerged from general anesthesia, we assessed the level of epidural blockade of all patients in both groups. Patients who complained of abdominal pain were excluded from this study, as it was considered that the epidural catheter had been inappropriately placed.

Postoperative pain management and assessment

Postoperatively, the epidural catheter was connected to both a patient-controlled analgesia (PCA) device (Bard, Bard, Mass., USA) and a continuous-infusion syringe pump (Terfusion, Terumo, Tokyo, Japan). Both settings were loaded with 0.4 mg of buprenorphine in 48 ml of 0.125% bupivacaine. The PCA setting allowed 4 ml of bolus administration with a lockout time of 30 min, and the infusion syringe pump was set at 1 ml·h^{-1} for the next 24 h. To quantify the severity of postoperative pain, the Pain Service Team, who were blinded as to which group the patient belonged to, asked the patients to rate their abdominal pain at rest and during movement, such as coughing and sitting up, using a 10-cm visual analog scale (VAS) graded from 0 (no pain) to 10 (the most severe pain imaginable) at 2, 24, and 48 h after surgery.

Cortisol measurement

Plasma cortisol concentration and urinary excretion were measured by fluorescence polarization immunoassay using the TDX system (Dainabot, Tokyo, Japan). Blood samples for assay were obtained before the surgical incision, at the end of surgery, and at 1 P.M. on the first postoperative day (1 POD). Urine samples for assay were collected during the operation and at 1 POD (5 A.M. to 1 P.M.).

Data analysis

Data are expressed as mean ± SEM. The demographic data were analyzed with Student's unpaired t-test. The differences between the two groups of the VAS were analyzed with the Mann-Whitney U test at each observation time. Attempt and injection times of the PCA were expressed as median and range. The differences between the groups were analyzed using the Mann-Whitney U test. Student's unpaired and paired t-tests were used for analysis of plasma cortisol concentration, urinary cortisol excretion, and blood pressure. A P value less than 0.05 was considered statistically significant.

Results

Patient characteristics did not differ between the groups, except for fluid and urine volume during sur-

Table 1. Patient characteristics (mean ± SEM)

Characteristic	Group E (n = 18)	Group G (n = 22)
Age (yr)	47.3 ± 2.0	46.6 ± 1.7
Weight (kg)	54.6 ± 2.3	53.5 ± 1.9
Duration of surgery (min)	100 ± 10	84 ± 8
Fluid volume during surgery (ml)	1956 ± 233*	1302 ± 85
Urine volume during surgery (ml)	302 ± 54*	146 ± 18
Urine volume on 1 POD[a] (ml)	1024 ± 140	887 ± 106

*$P < 0.05$ between the groups (unpaired t-test).
[a] First postoperative day (5 A.M. to 1 P.M.).

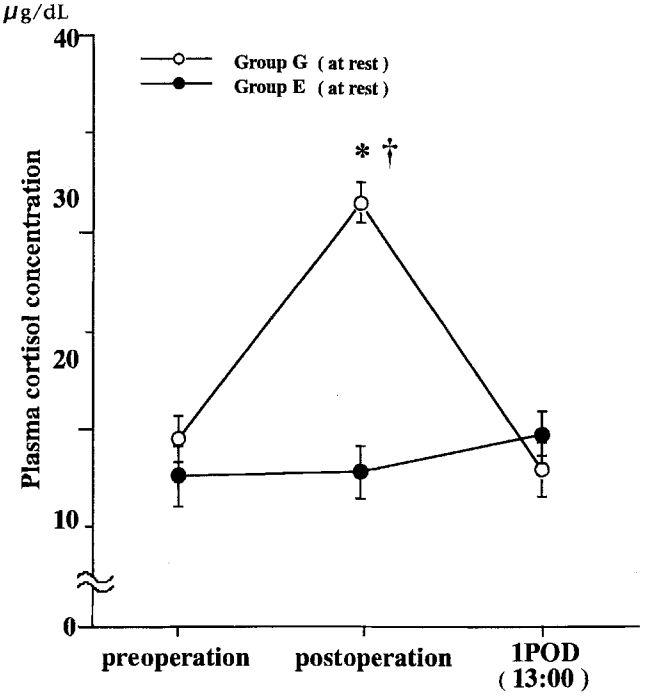

Fig. 1. Perioperative plasma cortisol concentrations. Values are mean ± SEM. *Group G*, general anesthesia group; *group E*, epidural anesthesia group. *$P < 0.05$ between the two groups; †$P < 0.05$ compared with preoperation. *1 POD*, First postoperative day

gery (Table 1). Since the level of blockade in all cases was above T7, and no patient complained of abdominal pain immediately after emergence from anesthesia, all patients were included for the subsequent data analysis. Although the systolic blood pressure and heart rate in group E did not change between pre- and postincision (Δ percent change, +1.6% and +2.7%, respectively), those in group G increased significantly immediately following the abdominal incision [Δ +26.1% and +9.5%, respectively). $P_{ET}CO_2$ in both groups was maintained between 33 and 40 mmHg throughout surgery.

Table 2. Patient-controlled analgesia, median (range) no. of times

	Group E (n = 18)	Group G (n = 22)
Attempt	7 (0–30)	9 (0–31)
Injection	6 (0–26)	6 (0–20)

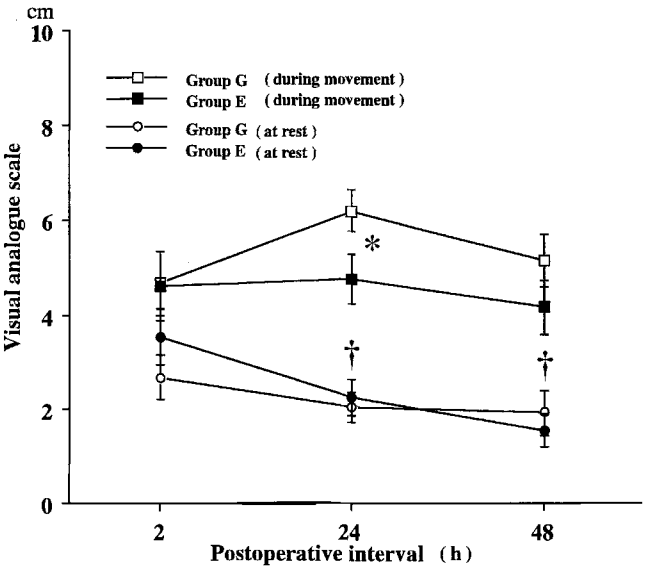

Fig. 2. Evaluation of postoperative analgesia by visual analogue scale at rest and during movement. Values are mean ± SEM. *Group G*, general anesthesia group; *group E*, epidural anesthesia group. *$P < 0.05$ between the two groups; †$P < 0.05$ compared with 2 h

Plasma cortisol concentration in group G increased significantly at the end of surgery and then decreased to the level of the preoperative period at 1 POD, whereas those in group E remained constant throughout the study period (Fig. 1). On the other hand, urinary cortisol excretion during surgery showed no significant differences between group E and group G (51 ± 11 and 39 ± 6 μg, respectively). Postoperative urinary cortisol excretion at 1 POD was significantly lower in group E than in group G (192 ± 34 *vs.* 480 ± 120 μg; $P < 0.05$).

All patients received 48 ml of 0.125% bupivacaine and 0.4 mg of buprenorphine over 48 h postoperatively by continuous infusion via an epidural catheter. There were no significant differences in attempt and injection times of PCA between the groups (Table 2). The VAS scores across the evaluation periods are depicted in Fig. 2. The VAS scores during movement at 24 h after surgery showed significantly better analgesia in group E than in group G, whereas the scores at the 2- and 48-h study periods did not differ between the two groups. There were no significant changes in VAS scores during movement in either study group over the

study period. The VAS scores at rest in both groups were significantly depressed at 24 and 48 h after surgery compared with the 2-h study period. No supplemental analgesic was required in either group during the study period.

Discussion

General anesthesia likely allows the entry of repeated afferent impulses into the spinal cord. Therefore, regional anesthesia may be more appropriate to show the preemptive effects clinically [5,6,17]. Indeed, we recently demonstrated that preincisional wound infiltration with lidocaine provided prolonged analgesia in patients undergoing hemorrhoidectomy even under spinal anesthesia [18]. The current study showed that sufficient epidural blockade throughout lower abdominal surgery resulted in the depression of urinary cortisol release and simultaneously better dynamic pain relief, at least at the first POD, compared with general anesthesia alone. Both study groups, however, showed similar VAS values during movement at 2 and 48 h following the surgery, suggesting that there were few effects of preemptive epidural analgesia on the level of pain in the immediate and late postoperative stages. This might be one of the reasons why the preemptive effects of epidural anesthesia still remain controversial.

The plasma cortisol concentration did not show concomitant changes with other parameters, such as pain scoring or analgesic requirement in the current study. We wonder if plasma cortisol is a useful indicator to express the stress condition during the postoperative period, when the intensity and duration of pain are variable and persistent [19,20]. Since the release and elimination of cortisol is a prompt response [21], measurement of plasma concentration at one point during the long-term postoperative period may not always reflect the actual intensity of stress at that moment. There is also good evidence that patients with Cushing's syndrome excrete cortisol into their urine in higher than normal amounts, even when plasma cortisol concentrations are within the normal range [22]. Therefore, to estimate the overall response of postsurgical stress in which the discharges of noxious stimuli are persistent, urinary excretion of cortisol may be a more rational indicator than plasma concentration. We found that urinary cortisol excretion in group E was significantly suppressed on 1 POD compared with group G, whereas plasma cortisol levels did not differ between the study groups.

It could be argued that epidural blockade during surgery in the current study was sufficient to suppress the entry of noxious stimuli into the spinal cord. Although we did not assess the level of epidural blockade before the surgical incision, this examination is not enough to verify that an appropriate blockade was maintained throughout surgery under general anesthesia. We therefore designed this study to exclude the patients who complained of abdominal pain with epidural administration of 8 to 10 ml of bupivacaine immediately after emergence from anesthesia. Furthermore, the concentration of sevoflurane was kept less than 0.5%, and ventilation was maintained spontaneously, so that we could have detected the patients' responses, such as tachypnea, when the surgical impact went beyond the range of epidural anesthesia. Concurrently, the plasma cortisol concentration at the end of surgery remained unchanged in group E, whereas it increased remarkably in group G. These findings suggest that epidural anesthesia in this study was able to achieve complete nearly complete suppression of noxious stimuli.

Although the differences in airway maintenance and ventilatory mode between the two groups may require brief mention, the $P_{ET}CO_2$, which was less than 40 mmHg throughout the surgery, excluded the effects of hypercapnia. Besides, the procedure of endotracheal intubation has been reported not to have significant effects on the release of cortisol [23]. Therefore, we believe that the differences in airway management during surgery were unlikely to have significant effects on cortisol release. Urine volume might be able to modify cortisol excretion. The greater amount of fluid-loading in group E than in group G to compensate for vasodilatation resulted in a higher volume of urine during the operation in group E than in group G. Since oliguria induces a delay in the urinary excretion of cortisol, the urinary excretion of cortisol in group G might have been greater than the results obtained in this study [24]. For ethical reasons, we administered 0.125% bupivacaine and buprenorphine epidurally to both study groups. This procedure might have modified the VAS values at the 2-h observation period.

In conclusion, the employment of sufficient epidural blockade prior to surgical stimuli and throughout lower abdominal surgery reduces the dynamic pain and stress response during the early postoperative period.

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