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Original contribution

Effects of intraoperative high-dose vs low-dose remifentanil for postoperative epidural analgesia after gynecological abdominal surgery: a randomized clinical trial☆,☆☆

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Abstract

Study objectives: To evaluate whether intraoperative high-dose remifentanil infusion increased local anesthetic consumption in postoperative epidural analgesia and postoperative pain scores compared with low-dose remifentanil infusion.

Design: Prospective, randomized controlled study.

Setting: Operating room, university hospital.

Patients: Thirty female patients scheduled for elective gynecological abdominal surgery.

Interventions: After epidural catheter placement and induction of general anesthesia, patients were randomly assigned to 2 anesthetic regimens. In the first group (high-dose remifentanil group), sevoflurane concentration was held constant at 1.2%, and the remifentanil infusion rate was titrated to maintain systolic blood pressure within 20% of baseline. In the second group (low-dose remifentanil group), the remifentanil infusion rate was held constant at 0.1 μg/(kg min), and the sevoflurane concentration was titrated to maintain systolic blood pressure within 20% of baseline. As abdominal wall closure began, 6 mL of 0.2% ropivacaine was administrated via epidural catheter; a patient-controlled analgesia device was set to deliver 4 mL/h of 0.2% ropivacaine with 3 μg/mL of fentanyl, with 2-mL incremental doses and a 15-minute lockout time.

Measurements: Local anesthetic consumption via postoperative epidural catheter and pain intensity with the Prince Henry pain scale were assessed for 48 hours after surgery.

Main results: The mean remifentanil infusion rate was 0.23 μg/(kg min) in the high-dose remifentanil group, 2.3 times the rate used in the low-dose remifentanil group. The cumulative amount of local anesthetic used within 48 hours of surgery was significant greater in the high-dose remifentanil group than in the low-dose remifentanil group (212 ± 25 mL vs. 181 ± 35 mL, respectively; $P < .05$), but postoperative pain scores were similar in each group.

Conclusions: Intraoperative high-dose remifentanil infusion increased local anesthetic consumption in postoperative epidural analgesia relative to low-dose remifentanil.

☆ Trial registration: University Hospital Medical Information Network UMIN000011185.

☆☆ Conflict of interest: All authors have no conflict of interest.

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Remifentanil, an analgesic agent widely used in general anesthesia, has a rapid onset and short duration of action [1]. This pharmacokinetic profile suggests that the discontinuation of remifentanil at the end of surgery may result in the rapid disappearance of analgesia. Therefore, appropriate postsurgical pain management is needed for immediate postoperative analgesia [2]. Moreover, acute exposure to high-dose remifentanil has been demonstrated to cause opioid-induced hyperalgesia (OIH) [3–10]. A previous study found that the intraoperative infusion of relatively high-dose remifentanil increased postoperative pain and morphine consumption for pain relief relative to low-dose remifentanil [3].

Epidural analgesia is an important postsurgical pain management strategy. Although it is typically used during both intraoperative and postoperative periods, epidural analgesia is sometimes used only in the postoperative period following remifentanil-based general anesthesia because of the intraoperative hemodynamic stability and excellent postoperative analgesia this protocol offers [11]. However, the intraoperative infusion of high-dose remifentanil may cause OIH. As a result, greater local anesthetic consumption in postoperative epidural analgesia for preventing OIH may be required. Therefore, we studied the intraoperative infusion of high-dose remifentanil in patients undergoing gynecological abdominal surgery to determine the effect on local anesthetic consumption in postoperative epidural analgesia and postoperative pain scores compared with low-dose remifentanil infusion.

1. Materials and methods

The protocol for this prospective, randomized study was reviewed and approved by the Institutional Research Ethics Committee of the University of Tsukuba Hospital (ethical approval reference no.: H21-360). We obtained written informed consent from all patients. The patient population consisted of women undergoing elective gynecological abdominal surgery with a lower abdominal incision below the umbilicus. Patients were all American Society of Anesthesiologists physical status grade 1-2 and between the ages of 20 and 69 years. Patients were excluded if they had diabetes, chronic pain, psychiatric illness, preoperative opioid analgesic use, or a history of drug or alcohol abuse or if they were unable to use a patient-controlled analgesia (PCA) device. Patients were also excluded if there were any contraindications to epidural catheter placement or if they refused epidural catheter placement.

On arrival in the operating room, an epidural catheter was placed at the T9-10, T10-11, or T11-12 interspaces, and a test dose of 3 mL of 1.5% lidocaine with epinephrine was administrated to exclude intrathecal or intravascular placement of the epidural catheter. General anesthesia was induced with propofol at 2 mg/kg, and tracheal intubation was facilitated with rocuronium at 0.6 mg/kg. Patients' lungs were then mechanically ventilated to normocapnia with sevoflurane in 50% oxygen/air. Intermittent boluses of rocuronium (0.2 mg/kg) were given until 30 minutes before the end of surgery based on the response to supramaximal train-of-4 stimulation of the thumb.

After induction of general anesthesia, patients were randomly assigned to 2 groups: a high-dose remifentanil group (H-group) and a low-dose remifentanil group (L-group). Simple randomization was performed by opening a sealed, opaque envelope after arrival in the operating room. In the H-group, the end-tidal sevoflurane concentration was maintained at 1.2% throughout anesthesia; a remifentanil infusion was started at 0.25 μg/(kg min) and subsequently increased or decreased by 0.05 μg/(kg min) to maintain systolic blood pressure within 20% of the baseline value. In the L-group, the remifentanil infusion was maintained at 0.1 μg/(kg min) throughout anesthesia; the end-tidal sevoflurane concentration was started at 2.0% and subsequently increased or decreased by 0.5% to maintain systolic blood pressure within 20% of the baseline value, but the end-tidal sevoflurane concentration was not decreased to less than 1.2% to prevent intraoperative awareness. Bispectral Index (BIS; Aspect Medical System, Norwood, MA) monitoring was used to confirm hypnotic levels during anesthesia.

Atropine (0.5 mg) or intermittent bolus of ephedrine (5 mg per bolus) was given as needed for bradycardia (heart rate <45 beats per minute) or hypotension (systolic blood pressure <80 mm Hg). Additional intravenous fluids were administered as deemed appropriate by the anesthesiologist in charge. At the start of abdominal wall closure, a 6-mL bolus dose of 0.2% ropivacaine was administrated via epidural catheter, and a standard PCA device (CADD Legacy PCA; Smiths Medical, UK) was set to deliver 4 mL/h of 0.2% ropivacaine with 3 μg/mL of fentanyl, with 2-mL incremental doses and a 15-minute lockout time. At the end of surgery, sevoflurane and remifentanil were discontinued, and residual neuromuscular blockade was antagonized with 2 mg of neostigmine and 1 mg of atropine. Patients were extubated when they could respond to verbal commands and breathe regularly with sufficient oxygenation. Patients were discharged from the surgical ward when they were alert and had stable vital signs. The epidural catheter location (T9-10, T10-11, or T11-12) was confirmed on a postsurgical abdominal radiograph.

Epidural analgesia using a PCA device was continued for 48 hours after surgery. Pain intensity was assessed at 4, 12, 24, 36, and 48 hours after surgery using the Prince Henry pain scale (0 = no pain while coughing; 1 = pain while coughing but not during deep breathing; 2 = pain during deep breathing but not at rest; 3 = pain at rest). If patients experienced grade 3 pain despite the use of incremental doses, the infusion rate was increased by 1 mL/h. If patients experienced grade 0 or 1 pain during 0-24 hours after surgery but suffered adverse effects (nausea, vomiting, or itching) related to epidural fentanyl, the infusion rate was decreased by 1 mL/h. If patients experienced only grade 0 or 1 on the pain scale during 24-48 hours after surgery, the infusion rate was decreased by 1 mL/h regardless