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Original contribution

Influence of high-dose intraoperative remifentanil with intravenous ibuprofen on postoperative morphine consumption in patients undergoing pancreaticoduodenectomy: a randomized trial☆

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Abstract

Study objective: High-dose remifentanil during surgery paradoxically increases postoperative pain intensity and morphine consumption. Cyclooxygenase inhibitors decrease prostaglandin synthesis, thereby antagonizing *N*-methyl-D-aspartate receptor activation, and may reduce hyperalgesia. This study was performed to evaluate whether postoperative morphine consumption increased following intraoperative continuous remifentanil infusion and whether this could be prevented by intravenous ibuprofen pretreatment.

Design: A randomized controlled study.

Setting: Single university hospital, study period from September 2014 to March 2015.

Patients: One hundred and twenty patients undergoing pancreaticoduodenectomy.

Interventions: After induction of anesthesia, patients received remifentanil target-controlled infusion (effect site concentration of 4 ng/mL or 1 ng/mL) with or without intravenous ibuprofen (800 mg).

Measurements: Postoperative cumulative total morphine consumption and pain intensity were assessed.

Main results: Intraoperative remifentanil use in patients receiving high-dose remifentanil was more than 3-fold higher than that in patients receiving low-dose remifentanil (2666.8 ± 858.4 vs 872.0 ± 233.3 μg, respectively; $P < .001$). However, cumulative total morphine consumption at postoperative 1, 3, 6, 12, 24, and 48 hours did not differ among the groups. There were no differences among the groups in the self-administered analgesic dose by the patients using a controlled analgesia device, number of self-administration attempts, numerical rating scale for pain, or analgesic side effects.

Conclusions: We found no influence on postoperative pain after high-dose remifentanil in patients undergoing pancreaticoduodenectomy. Addition of intravenous ibuprofen did not reduce postoperative morphine consumption or pain intensity.

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1. Introduction

Opioids are commonly used as analgesics during the perioperative period. However, previous studies have indicated increased pain intensity following intraoperative use of opioids [1]. Remifentanil is an ultra-short-acting opioid that is metabolized by tissue and plasma esterases. Because of its profile of rapid onset and rapid recovery, it is widely used intraoperatively. However, intraoperative high-dose remifentanil paradoxically increases postoperative pain intensity and morphine consumption [2-6].

The mechanism underlying opioid-induced hyperalgesia (OIH) is still not clear, but it has been suggested to be mediated by central sensitization involving *N*-methyl-D-aspartate (NMDA) receptors [5,7,8]. Prostaglandin stimulates glutamate release in astrocytes and the spinal cord dorsal horn following NMDA receptor activation [9,10]. Cyclooxygenase (COX) inhibitors decrease prostaglandin synthesis, thereby antagonizing NMDA receptor activation and reducing hyperalgesia [11-15]. Intravenous ibuprofen has recently been used to reduce pain intensity and morphine consumption perioperatively [16]. This study was performed to evaluate whether postoperative morphine consumption increased following intraoperative continuous remifentanil infusion and whether this could be prevented by intravenous ibuprofen pretreatment. We hypothesized that intravenous ibuprofen would reduce postoperative pain intensity and morphine consumption in patients receiving a continuous infusion of high-dose remifentanil during pancreaticoduodenectomy.

2. Methods

Ethical approval for this study (institutional review board number 1402-050-555) was provided by the institutional review board of Seoul National University Hospital, Seoul, Korea (Chairperson Prof Jaeseung Baek) on 19 March 2014. The study protocol was registered at ClinicalTrials.gov (NCT02243254). Written informed consent was obtained from all patients enrolled in the study. The inclusion criteria were an age of 18 to 80 years and scheduled for elective pancreaticoduodenectomy. There were no important changes to the methods after commencement of the trial. The exclusion criteria were chronic pain, psychiatric disease, renal dysfunction, allergy to nonsteroidal anti-inflammatory drugs, history of drug addiction, pregnancy, or inability to use a patient-controlled analgesia (PCA) device. In total, 120 patients were included in the study between September 2014 and March 2015.

2.1. Randomization

This was a double-blind, randomized study conducted in Seoul National University Hospital, a tertiary hospital in Seoul, Korea. Eligible patients were randomly allocated to 1 of 4 groups: high-dose remifentanil with or without intravenous ibuprofen (Caldolor 800 mg) and low-dose remifentanil with or without intravenous ibuprofen. The randomization sequence was created with a 1:1:1:1 allocation using a random block size of 8. The random list was generated by a statistician who was not involved in the study. All patients, medical personnel, and investigators were blinded to the group allocations, which were placed in sealed opaque envelopes on initial randomization. Treatment allocation was concealed from patients, researchers, and the statistician. An independent nurse prepared the study for the respective groups.

2.2. Study protocol and anesthetic regimen

All patients received standard perioperative care. Anesthesia was induced with intravenous propofol (2 mg/kg) and rocuronium (0.8 mg/kg). Anesthesia was maintained with sevoflurane and remifentanil target-controlled infusion (TCI) (Orchestra with Base Primea; Fresenius Kabi, Paris, France). The bispectral index was maintained between 40 and 60. After induction of anesthesia, patients were allocated to 1 of the following regimens: the LR group received remifentanil to reach a target effect-site concentration of 1 ng/mL and saline placebo; the LRI group received remifentanil using TCI to reach a target effect-site concentration of 1 ng/mL and intravenous ibuprofen (800 mg) over 30 minutes; the HR group received remifentanil to reach a target effect-site concentration of 4 ng/mL and saline placebo; and the HRI group received remifentanil to reach a target effect-site concentration of 4 ng/mL and intravenous ibuprofen (800 mg) over 30 minutes. The PCA device (AutoMed 3200; Ace Medical, Seoul, Korea) was connected to the venous line and started 30 minutes before the end of surgery. After extubation, patients were transferred to the recovery room. The PCA device was programmed to deliver basal infusion of morphine at 2 mg/h and a bolus dose of 1 mg of morphine at a lockout interval of 15 minutes. The PCA device was continued for at least 48 hours. If the PCA analgesia was ineffective, supplemental rescue boluses of 50 μg intravenous fentanyl were administered. The PCA device running time, number of times the patient pressed the PCA button, self-administered PCA bolus dose, and total infused volume of drugs were electronically collected from the PCA device. Postoperative pain intensity was assessed until 48 hours after surgery by independent nurses who were blinded to the study groups using a numerical rating scale (NRS) (0-10, where 0 = no pain and 10 = extreme pain).

2.3. Statistical analysis

The primary end point was cumulative morphine consumption at 48 hours postoperatively. The secondary end point was pain intensity measured on the NRS. In a study by Joly et al [5], the increase in 48-hour cumulative morphine consumption was 18 (59-109) mg when using high-dose remifentanil. Taking a 50% decrease in the increase of morphine