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Original Contribution

The effect of a continuous infusion of low-dose esmolol on the requirement for remifentanil during laparoscopic gynecologic surgery

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Abstract

Study Objective: To investigate whether a continuous infusion of low-dose esmolol results in an opioid-sparing effect during surgery.

Design: Randomized, double-blinded, placebo-controlled clinical comparison study.

Setting: Operating room of a university hospital.

Patients: 56 ASA physical status 1 and 2 patients, aged 20 to 60 years, undergoing laparoscopic gynecologic surgery of less than two hours' duration.

Interventions: The esmolol group (n = 28) received a 0.5 mg/kg loading dose of esmolol followed by an infusion of esmolol 30 μg/kg/min; the saline group (n = 28) received equivalent volumes of normal saline.

Measurements: The effect-site concentration of remifentanil (ng/mL) to maintain adequate anesthetic depth before infusion of the study drug (before-concentration) was measured. During infusion of study drug, the effect-site concentration of remifentanil was adjusted every 5 minutes to maintain systolic blood pressure within 15% of baseline and a Bispectral Index value between 50–60. The average of these adjusted concentrations (after-concentration) was measured and compared to the before-concentration. The quality of postoperative recovery was assessed.

Main Results: In the esmolol group, the after-concentration of remifentanil was decreased by 33.3% compared with the before-concentration. The total dose of remifentanil infused was also lower in the esmolol group (0.09 ± 0.1 vs 0.14 ± 0.03 μg/kg/min; $P = 0.031$). The esmolol group had lower scores on a pain numerical rating scale and required less fentanyl in the Postanesthesia Care Unit.

Conclusions: Intraoperative esmolol infusion decreases both the requirement for remifentanil and postoperative administration of rescue analgesics.

1. Introduction

Esmolol, a beta-blocker, is used to stabilize the cardiovascular response during the perioperative period. It effectively blocks undesirable cardiovascular responses

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during endotracheal intubation and extubation [1,2], and is also used for treating tachyarrhythmias such as supraventricular tachycardia [3]. In addition, evidence indicates that esmolol affects antinociception [4–7] and obtunds the bispectral index (BIS) response [8,9]. These findings have led to many studies about the dose-sparing effects of beta-blockers on inhalation anesthetics and opioids in the perioperative period. Johanson et al. [10] reported that intraoperative continuous infusion of esmolol reduced the minimum alveolar concentration of isoflurane. White et al [11] and Collard et al [12] showed that perioperative esmolol administration reduced the required amount of fentanyl, which is used as a rescue analgesic in the recovery room. Intraoperative administration of beta-blocker would seem to affect the amount of opioid requirement for maintaining adequate anesthetic depth during surgery. Also, it is expected that beta-blockers would make any difference on the speed and quality of postanesthetic recovery by changing the amount of intraoperative opioid administration. However, there have been only a few studies on the relationship between beta-blockers and the requirement for opioids during surgery, and these did not present clinically applicable information.

We performed this study to identify the effects of an intraoperative continuous infusion of low-dose esmolol on the required effect-site concentration of remifentanil for adequate anesthetic depth and on postanesthetic recovery.

2. Materials and methods

The study was conducted on 56 ASA physical status 1 and 2 patients aged between 20 and 60 years, undergoing laparoscopic gynecologic surgery that lasted less than 2 hours, between December 2009 and May 2010. The institutional review board of our hospital approved this double-blinded, randomized, placebo-controlled study, and participants provided written consent. We excluded patients with cardiovascular diseases such as hypertension, arrhythmia, or myocardial ischemia; unstable hemodynamics due to hemorrhage, hypovolemia, or loss of body fluids; asthma or chronic obstructive pulmonary diseases; allergies to the study drug; or BMI under 16 kg/m^2 or over 30 kg/m^2, as well as patients requiring opioids for pain diseases and those who refused to participate. An anesthesiologist not involved in the care of the patients prepared the covered syringe pump for esmolol and placebo solutions, and held the randomization codes until the end of the study. Another anesthesiologist, who was not involved with postoperative pain evaluation and was blinded to group allocation, conducted the anesthesia. Patients and the anesthesiologist were blinded to group allocation for the duration of the study.

Intraoperative monitoring included three-lead electrocardiography, non-invasive blood pressure (BP), pulse oximetry, expired CO_2, pharyngeal temperature, and urine output. Once baseline values had been obtained, anesthesia was induced with 2.0 mg/kg propofol and 0.5 mg/kg atracurium. Following loss of consciousness, sevoflurane (input concentration 2–5 vol%) with 100% O_2 was inhaled for 90 seconds according to the cardiovascular response of the patient, and endotracheal intubation was performed. Ventilation was mechanically controlled and adjusted to maintain end-tidal CO_2 at 30–35 mmHg. Anesthesia was maintained with sevoflurane (input concentration 2.0 vol%), 3 L/min medical air, 1 L/min oxygen using a same semi-closed circuit system, and 2.0 ng/mL of remifentanil in an effect-site concentration target-controlled infusion provided by a computer-assisted continuous infusion system (Orchestra® Base Primea; Fresenius Vial, Grenoble, France). Atracurium (5 μg/kg/min) was infused for muscle relaxation. Ringer's lactate was infused at 6 mL/kg/hr during surgery. In the case of bleeding, 6% hydroxyethyl starch of the same volume as blood loss was infused.

The effect-site concentration (ng/mL) of remifentanil required to maintain an adequate anesthetic depth was determined 30 minutes after establishing pneumoperitoneum and the start of the surgical manipulation, as initial skin incision and establishing pneumoperitoneum had an effect on BP and 30 minutes was considered to be sufficient to reach a steady-state condition. We defined the adequate anesthetic depth as when 1) the systolic blood pressure (SBP) measured every minute was maintained within 15% of the baseline value for three consecutive measurements, and 2) the BIS value was maintained at 50–60. The effect-site concentration of remifentanil to maintain this adequate depth was defined as the 'before-concentration'.

Subsequently, the esmolol group (n = 28) was infused with a 0.5 mg/kg loading dose of esmolol followed by an infusion of 30 μg/kg/min, and the saline group (n = 28) was infused with normal saline of the same volume. Starting infusion of the study drug, BP and BIS value were measured every 5 minutes, and the effect-site concentration of remifentanil was increased or decreased by 0.2 ng/mL if a BIS outside the range of 50–60 was recorded for more than 30 seconds, or SBP varied by more than 15% from the baseline value or was > 150 mmHg or < 90 mmHg. When the heart rate (HR) was < 50 bpm or SBP was < 80 mmHg, atropine (0.5 mg) or ephedrine (5 mg) was injected respectively, and such cases were excluded from the study. As the surgeon began intraperitoneal irrigation, the infusion of muscle relaxant was discontinued. When the trocar was removed from the abdominal wall, administration of sevoflurane, remifentanil, and esmolol were stopped, and the total dose of these drugs infused during anesthesia was recorded. The mean effect-site concentration of remifentanil during study drug infusion was calculated, and defined as the 'after-concentration'.

In all patients, 4 mg of ondansetron was injected 30 minutes before the end of surgery. Neuromuscular block was reversed with 0.4 mg glycopyrrolate and 10 mg pyridostigmine. The train-of-four ratio was measured and the patients were extubated.