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Pain

# Preoperative butorphanol and flurbiprofen axetil therapy attenuates remifentanil-induced hyperalgesia after laparoscopic gynaecological surgery: a randomized double-blind controlled trial

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## Abstract

**Background:** Several studies indicate that remifentanil exposure may engender opioid-induced hyperalgesia. Butorphanol and flurbiprofen axetil are proposed as adjunctive analgesics for postoperative pain control. This randomized double-blind controlled study was designed to investigate the antihyperalgesic effects of butorphanol combined with flurbiprofen axetil on opioid-induced hyperalgesia.

**Methods:** One hundred and twenty patients undergoing elective laparoscopic gynaecological surgery with sevoflurane anaesthesia were randomized to one of four groups, as follows: intraoperative sufentanil 0.30 μg $kg^{-1}$ (Group S); remifentanil 0.30 μg $kg^{-1}$ $min^{-1}$ (Group R); intraoperative remifentanil and pre-anaesthesia butorphanol 20 μg $kg^{-1}$ (Group B); or intraoperative remifentanil and pre-anaesthesia butorphanol 10 μg $kg^{-1}$ combined with flurbiprofen axetil 0.5 mg $kg^{-1}$ (Group BF). Sufentanil was used to control postoperative pain. The threshold and area of postoperative mechanical hyperalgesia were measured with Von Frey filaments. Pain intensity, sufentanil consumption, and side-effects were recorded for 24 h after surgery.

**Results:** Compared with Group S, remifentanil anaesthesia increased the pain score, postoperative sufentanil consumption, and area of hyperalgesia [mean 49.9 (SD 8.6) *vs* 60.5 (10.0) $cm^2$, $P<0.001$] and reduced the hyperalgesia threshold on the dominant inner forearm [mean 89.5 (SD 23.4) *vs* 60.6 (22.6) g, $P=0.004$]. Compared with Group R, the pain score, sufentanil consumption, and area of hyperalgesia were reduced and hyperalgesia threshold was elevated likewise in Groups B and BF. However, the efficacy in Group BF was higher than in Group B ($P=0.021$).

**Conclusions:** The preoperative combination of butorphanol and flurbiprofen axetil effectively ameliorated opioid-induced hyperalgesia in patients undergoing laparoscopic gynaecological surgery under sevoflurane–remifentanil anaesthesia.

**Clinical trial registration:** NCT02043366.

**Key words:** analgesics; opioid; remifentanil; complications; hyperalgesia; cyclo-oxygenase inhibitors; flurbiprofen axetil; opioid mixed agonist-antagonists; butorphanol; pain threshold

Remifentanil is commonly used in analgesia during general anaesthesia.[1 2] However, several studies suggest that intraoperative remifentanil infusion may be responsible for postoperative opioid-induced hyperalgesia (OIH), a paradoxical state of hypersensitivity to nociceptive stimuli.[3–7] Although the specific mechanism and clinical significance of OIH remain controversial,[8 9]

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**Editor's key points**

- Opioid-induced hyperalgesia (OIH) may be problematic after remifentail anaesthesia, with strategies needed to reduce it.
- Inhibition of cyclo-oxygenase, combined with a κ agonist, may target some of the underlying mechanisms.
- This randomized controlled trial found a reduction in mechanical hyperalgesia with flurbiprofen and butorphanol.
- Further studies are needed on remifentanil-induced OIH and targeted strategies to minimize its clinical impact.

the phenomenon has been implicated in chronic postsurgical pain and, possibly, in chronic pain treatment with opioids.[10–14] Therefore, prevention of OIH in surgical patients may improve clinical care and deserves further clinical investigation.

Several experimental and clinical reports suggest that cyclo-oxygenase inhibition ameliorates OIH in animals, human volunteers, and patients.[15–19] However, cyclo-oxygenase inhibitors have potential drawbacks and must be administered with discretion in patients with active peptic ulcer, recent gastrointestinal bleeding, renal dysfunction, pregnancy, or allergy to aspirin.

Butorphanol has both spinal analgesic and sedative functions because of predominantly central κ-receptor agonist activation.[20–22] Furthermore, antihyperalgesic activity and potency of κ opioids have been reported in various acute pain models.[23–25] Butorphanol and the cyclo-oxygenase inhibitor flurbiprofen axetil (FA) are proposed as adjunctive pre-anaesthetics and analgesics for postoperative pain control. However, no report has focused on the antihyperalgesic efficacy of butorphanol or butorphanol combined with FA in OIH in the clinical setting.

The objective of the study was to verify the hypothesis that butorphanol combined with FA administration can prevent intraoperative remifentanil infusion-induced hyperalgesia in patients undergoing laparoscopic gynaecological surgery with sevoflurane anaesthesia. We selected a modified threshold of the mechanical hyperalgesia on the dominant inner forearm before and 24 h after surgery as the primary outcome. Pain intensity, cumulative sufentanyl consumption, hyperalgesia area and threshold around the incision, and side-effects were the secondary outcomes investigated for 24 h after surgery.

## Methods

### Ethical approval and study population

The study was approved by the Tianjin Medical University General Hospital Ethic Committee (Tianjin, China; approval number IRB2013-077-01), and the study protocol was registered (www.clinicaltrials.gov; Identifier: NCT02043366; the current manuscript is part of a larger study). We contacted patients aged 20–60 yr, with ASA physical status I–II, who were to undergo laparoscopic ovarian cyst resection. Written informed consent was obtained from all the subjects. The exclusion criteria were as follows: bronchial asthma; coronary heart disease; severe hypertension; diabetes mellitus; obesity (BMI >30 kg $m^{-2}$); cardiac, hepatic, and renal dysfunction; psychiatric disease; history of chronic pain;history of alcohol or opioid abuse; chronic use of opioids; intake of any analgesic within 48 h before surgery; pregnancy; allergy and contraindication to butorphanol or nonsteroidal anti-inflammatory drugs; history of gastrointestinal disease (peptic ulcer disease, Crohn's disease, or ulcerative colitis); contraindication for the use of patient-controlled analgesia (PCA); or incapacity to comprehend pain assessment. After randomization and allocation, patients were withdrawn if laparoscopy was converted to open surgery or if they required reinvestigation for postoperative bleeding.

### Procedures and outcomes

Patients were randomly divided into one of four groups, as follows: (i) patients in Group S received intraoperative sufentanil 0.30 μg $kg^{-1}$ and placebo (normal saline, similar volume of butorphanol) before induction of anaesthesia; (ii) patients in Group R received intraoperative remifentanil 0.30 μg $kg^{-1}$ $min^{-1}$ and placebo before induction of anaesthesia; (iii) patients in Group B received intraoperative remifentanil 0.30 μg $kg^{-1}$ $min^{-1}$ and butorphanol (Hengrui Medicine Co., Jiangsu, China) 20 μg $kg^{-1}$ (clinical dosage) before induction of anaesthesia; and (iv) patients in Group BF received intraoperative remifentanil 0.30 μg $kg^{-1}$ $min^{-1}$ and butorphanol 10 μg $kg^{-1}$ combined with FA (Tide Pharmaceutical Co., Beijing, China) 0.5 mg $kg^{-1}$ before induction of anaesthesia. Patients were randomly assigned to treatment regimens based on a randomization list provided by the Department of Anaesthesiology, Tianjin Medical University General Hospital according to the relevant Standard Operating Procedure (computer-generated random number system). The allocation sequence was concealed until after consent was obtained. Patients and a treating anaesthetist involved in the perioperative management were blinded to the group assignment. Primary and secondary outcomes were analysed and recorded by another anaesthetist responsible for the data collection but not directly involved in the treatment of the patient and who was blinded to randomization.

On the day before surgery, all the patients were instructed to use a PCA device and were evaluated for pain on a 11-point numerical rating scale (NRS): 0=no pain; and 10=worst pain imaginable. The baseline mechanical nociceptive threshold was assessed using 20 hand-held Von Frey filaments (North Coast Medical Inc., Gilroy, CA, USA) in an area 2–5 cm around the incision at 12 predefined positions in all four directions and on the dominant inner forearm according to the published method.[5 6 26–29] Every position was measured three times at intervals of ~15 s, and a mean value was calculated for statistical analysis.[5 28 29] The mechanical hyperalgesia threshold was defined as the smallest force (in grams) necessary to bend a Von Frey filament that was detected as painful by the patient. The test was performed again at 24 h after surgery.

Upon arrival at the operating room, the patients were generally monitored by non-invasive blood pressure, ECG, heart rate (HR), pulse oximetry, and bispectral index. A peripheral i.v. line in the left arm and urinary catheter were attached before induction of anaesthesia.

General anaesthesia was induced with midazolam 0.05 mg $kg^{-1}$, sufentanil 0.2 μg $kg^{-1}$, and propofol 2 mg $kg^{-1}$, and tracheal intubation was facilitated with rocuronium 0.7 mg $kg^{-1}$. After intubation, all the patients were mechanically ventilated [end-tidal carbon dioxide values of 35–45 mm Hg (1 mm Hg=0.133 kPa)]. Anaesthesia was maintained with sufentanil injection before skin incision or continuous remifentanil infusion (RenFu Co., Hubei, China) as an intraoperative analgesic, and administration of sevoflurane (Maruishi Pharmaceutical Co., Osaka, Japan) as an initial 1.3 minimal alveolar concentration (MAC) and oxygen–air mixture (fraction of oxygen, 50%). The depth of anaesthesia was adjusted during surgery by 1% stepwise titration of sevoflurane, based on targeting bispectral index (40–60) and haemodynamic changes: HR exceeding pre-induction values by 15% and mean arterial blood pressure (MAP) exceeding baseline