BJA

British Journal of Anaesthesia, 119 (4): 792–802 (2017)

doi: 10.1093/bja/aex174
Clinical Practice

CLINICAL PRACTICE

Low-dose buprenorphine infusion to prevent postoperative hyperalgesia in patients undergoing major lung surgery and remifentanil infusion: a double-blind, randomized, active-controlled trial

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Abstract

Background. Postoperative secondary hyperalgesia arises from central sensitization due to pain pathways facilitation and/or acute opioid exposure. The latter is also known as opioid-induced hyperalgesia (OIH). Remifentanil, a potent μ-opioid agonist, reportedly induces postoperative hyperalgesia and increases postoperative pain scores and opioid consumption. The pathophysiology underlying secondary hyperalgesia involves N-methyl-D-aspartate (NMDA)-mediated pain pathways. In this study, we investigated whether perioperatively infusing low-dose buprenorphine, an opioid with anti-NMDA activity, in patients receiving remifentanil infusion prevents postoperative secondary hyperalgesia.

Methods. Sixty-four patients, undergoing remifentanil infusion during general anaesthesia and major lung surgery, were randomly assigned to receive either buprenorphine i.v. infusion (25 $\mu g\ h^{-1}$ for 24 h) or morphine (equianalgesic dose) perioperatively. The presence and extent of punctuate hyperalgesia were assessed one day postoperatively. Secondary outcome variables included postoperative pain scores, opioid consumption and postoperative neuropathic pain assessed one and three months postoperatively.

Results. A distinct area of hyperalgesia or allodynia around the surgical incision was found in more patients in the control group than in the treated group. Mean time from extubation to first morphine rescue dose was twice as long in the buprenorphine-treated group than in the morphine-treated group: 18 *vs* 9 min ($P=0.002$). At 30 min postoperatively, patients receiving morphine had a higher hazard ratio for the first analgesic rescue dose than those treated with buprenorphine ($P=0.009$). At three months, no differences between groups were noted.

Conclusions. Low-dose buprenorphine infusion prevents the development of secondary hyperalgesia around the surgical incision but shows no long-term efficacy at three months follow-up.

Key words: secondary hyperalgesia; remifentanil; buprenorphine; postoperative; thoracic surgery

Editorial decision March 29, 2017; **Accepted:** May 16, 2017

Editor's key points

- Opioid-induced hyperalgesia (OIH: paradoxical increase in pain from opioids) may be problematic postoperatively.
- Buprenorphine may reduce OIH due to central, non-opioid receptor effects.
- Hyperalgesia after perioperative buprenorphine was compared to morphine after thoracic surgery.
- Buprenorphine resulted in less postoperative hyperalgesia than morphine
- Further studies are needed to improve diagnosis and management of acute OIH.

Hyperalgesia is clinically defined as an increased pain sensation following a stimulus that normally provokes pain. Primary hyperalgesia occurs as a response to a noxious stimulation, such as trauma or surgical incision, arises from peripheral nociceptor sensitization and is limited to the damaged area. Secondary hyperalgesia manifests far from the surgically damaged area and is thought to be due to central sensitization. Opioid-induced hyperalgesia (OIH), namely nociceptive sensitization induced by exposure to opioids, is part of secondary hyperalgesia.[1–3] OIH follows opioid analgesia and may last long after withdrawal.[2]

Among the various μ-opioid agonists, remifentanil is a potent and ultra-short-acting opioid widely used during general anaesthesia. On withdrawal, even after short-term infusion, remifentanil may induce hyperalgesia in the area surrounding the surgical site[4] and increase postoperative opioid consumption.[4–6] Experimental studies have also described remifentanil-induced hyperalgesia in healthy subjects.[7]

Although the mechanisms underlying secondary hyperalgesia and OIH remain unclear, some attribute a key role to N-methyl-D-aspartate (NMDA)-related pain facilitation.[8 9] Experimental and clinical studies in animals and humans have shown that NMDA-receptor antagonists prevent the development of secondary hyperalgesia and OIH.[2 4 10 11] Like ketamine,[11 12] another NMDA receptor antagonist frequently used in experimental studies, buprenorphine also seems to counteract remifentanil-induced hyperalgesia at small doses (0.15 mg i.v.).[13] Possible explanations for buprenorphine anti-hyperalgesia include its k-receptor antagonism that may block pro-nociceptive NMDA-mediated activity through a dynorphin-mediated mechanism,[13 14] altered spinal dynorphine levels,[15] downregulation of δ-receptors[16] and enhanced descending facilitation.[14] Buprenorphine abolishes remifentanil-induced post-infusional hyperalgesia in healthy volunteers undergoing transcutaneous electrical stimulation.[13] It also has a broad analgesic profile and offers the opportunity to treat different pain phenotypes, including neuropathic pain symptoms.[17] No data yet show whether buprenorphine infused continuously at a low dose could prevent secondary hyperalgesia and OIH after surgical procedures, especially after those with an increased risk of developing chronic pain postoperatively such as major lung surgery.[18] This information would help in preventing postoperative hyperalgesia and/or allodynia, thus reducing the patient's acute postoperative discomfort and possibly reducing the risk of postoperative chronic pain. Thoracotomy is considered one of the surgical procedures at the highest risk of postoperative persistent pain (>3 months). The incidence of moderate/severe thoracic pain at 1 yr following thoracotomy is between 11–30% and 3–5%, respectively.[18–20] Usually, in most patients, post-thoracotomic pain is severe until 1 month postoperatively, then gradually decreases at 1 yr postoperatively.[19]

In this double-blind, randomized, active-control trial, we investigated whether low-dose buprenorphine infusion prevents or reduces secondary hyperalgesia after major lung surgery. To do so, before inducing general anaesthesia in patients undergoing thoracotomy, we started a low-dose buprenorphine i.v. infusion and assessed, as primary endpoints, the presence and extension of postoperative punctuate hyperalgesia measured by quantitative sensory testing (QST). As secondary outcomes, we collected postoperative pain scores, opioid consumption and postoperative neuropathic pain at one and three months after surgery. Control patients underwent the same general anaesthesia but instead of buprenorphine received an equianalgesic morphine infusion.

Methods

Patient selection and study design

This single-centre, double-blind, prospective, randomized, active-control trial was conducted after local Institutional Review Board approval and in accordance with good clinical practice and the guidelines set out in the Declaration of Helsinki. Informed consent was obtained from each patient. Eligible patients undergoing major lung surgery under the same, experienced surgeon were consecutively included in this trial from the Department of Thoracic Surgery at our university teaching hospital. The trial was registered on Current Controlled Trial (http://www.controlled-trials.com/) with number ISRCTN91017061.

Eligible patients met the following inclusion criteria: age 18 yr or older; ASA class I–III; planned, open, unilateral lung surgery by lateral thoracotomy; and the express refusal to undergo intraoperative or postoperative thoracic epidural analgesia. Exclusion criteria included: extremely high or low weight (less than 40 kg and greater than 100 kg); known opioid drug abuse; ongoing chronic opioids and/or antidepressant and/or anticonvulsive treatment; inability to manage a patient-controlled analgesia (PCA) device; moderate-to-severe pre-existing chronic obstructive pulmonary disease [forced expiratory volume in 1 s (FEV1) <50% predicted]; chronic renal insufficiency; diabetes; or peripheral neuropathy.

During preoperative assessment, all patients that were enrolled were informed about the study objectives and protocol, and were shown how to use a visual analogue scale (VAS), a PCA device and received a demonstration of QST. Patients were randomly allocated using an online research randomizer (https://www.randomizer.org) into two groups (32 patients each) to receive intraoperative and postoperative continuous infusion of low-dose buprenorphine (25 μg h^{-1}, Temgesic®, Schering-Plough SpA, Italy) or an equianalgesic, control infusion of morphine (834 μg h^{-1}, morphine chlorhydrate, Molteni Farmaceutici, Italy; 0.3 mg of i.v. buprenorphine was considered equianalgesic to 10 mg of i.v. morphine).[21] Each drug infusion was prepared in an elastomeric infusor (Infusor SV2 System, flow rate: 2 ml h^{-1}; Baxter International Inc., Deerfield, Illinois, USA) by a nurse blinded to the study protocol, and both drugs were diluted in NaCl 0.9% up to a final buprenorphine concentration of 12.5 μg ml^{-1} and a morphine concentration of 417 μg ml^{-1}. Drug infusion was started at anaesthesia induction and discontinued 24 h later. The infusion was not labelled.