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.

Nurses in charge of postoperative care and staff members who collected the data were blinded to the study protocol and randomization.

General anaesthesia and postoperative analgesia

Anaesthetic management was standardized for all study patients. All patients received the same i.v. premedication 1 h before surgery (midazolam 0.02 mg kg^{-1}, ketorolac 15 mg, paracetamol 1 g) and the same remifentanil-based general anaesthesia, supplemented with oxygen and desflurane. A commercial target-controlled infusion (TCI) pump (Alaris PK Syringe Pump, Cardinal Health, Rolle, Switzerland) was used to control the effect-site TCI of remifentanil according to a pharmacokinetics model.[22] In both groups, in patients breathing oxygen, anaesthesia was induced with propofol (2–2.5 mg kg^{-1}) and a remifentanil TCI to obtain a predicted site-effect concentration of 5 ng ml^{-1}. Tracheal intubation with a double lumen tube was facilitated with cis-atracurium (0.15 mg kg^{-1}). Anaesthesia was then maintained with desflurane, oxygen mixed with air and remifentanil TCI of 4 ng ml^{-1}. Continuous ECG, invasive arterial blood pressure, plethysmographic oxygen saturation, end-tidal carbon dioxide and desflurane concentrations were monitored using an S/5 anaesthesia monitor (GE Datex-Ohmeda, Helsinki, Finland). Approximately 30 min before surgery ended, all patients received an i.v. bolus of morphine (150 μg kg^{-1}). Once extubated, patients were transferred to the post-anaesthesia care unit (PACU) for 2 h where a nurse blinded to the study protocol administered i.v. morphine titrated to reach a VAS score $\leq$3 (3 mg of morphine every 5 min), before connecting each patient to a PCA device (Gemstar, Abbott, North Chicago, IL, USA) containing morphine 0.5 mg ml^{-1} (bolus dose, 1 mg; lockout time, 7 min; maximum dose allowed in 4 h, 20 mg). Pre-PCA opioid consumption was assessed by measuring time from extubation to first morphine rescue dose (in the first 30 postoperative minutes) and total morphine titration dose required to reach a VAS score $\leq$3. In addition to PCA, according to a multimodal postoperative analgesic regimen routinely used at our institution, each patient received 1 g of paracetamol every 6 h and 30 g of ketorolac every 8 h during the first postoperative day. After surgery ended, as secondary outcomes, a nurse blinded to the study protocol and randomization collected VAS scores at rest and during coughing at 8, 16, 24 and 48 h, total morphine PCA consumption, blood–gas analysis values, and the incidence of postoperative nausea and vomiting (PONV) at 24 h.

QST

QST took place in a quiet room kept at a constant temperature (22 °C). On the day before surgery, the same investigator tested all of the patients to assess pain and tactile thresholds at the site of the probable surgical incision (between the T5 and T6 ribs along the mid-axillary line) and at the corresponding area on the contralateral side. On the day after surgery, each patient was evaluated to determine four QST variables: changes in static mechanical pain perception threshold on the operated side (1 cm away from and around the surgical incision) and on the contralateral side, and the existence and size of hyperalgesic and allodynic areas around the surgical incision. The contralateral side was always probed first, both before and after surgery.

The tactile threshold for punctuate mechanical stimuli was assessed using 20 calibrated (0.008–300 g mm^{-2}) von Frey filaments (NC-17775 Von Frey® Filaments, Bioseb, Chaville, France). The von Frey filaments were applied in ascending order of stiffness, with approximately 10 s elapsing between two successive stimuli, to avoid temporal summation.[23] The tactile threshold was defined as the smallest force (g mm^{-2}) necessary to bend a von Frey hair, and perceived by the patient as three consecutive skin touches. If the tactile pain threshold exceeded hair number 6.65 (300 g mm^{-2}), skin sensitivity was censored at that number.

The pain threshold for punctuate mechanical stimuli was assessed with the same set of von Frey filaments and the same procedures, and defined as the smallest force necessary to bend a filament, and perceived by the patient as three consecutive painful stimuli.

The hyperalgesic area around the surgical incision was measured by modifying a previously described method.[24–26] Each patient was tested with the von Frey filament that in postoperative pain threshold testing evoked pain on the opposite side. Stimulation was started far from the surgical incision and moved toward the incision in 1 cm steps until the patient reported a distinct change in pain perception. The first point at which the patient reported a more painful, sore or sharp feeling was marked, and the distance to the incision was measured (Fig. 6). Finally, we calculated the incidence and extension of peri-incisional mechanical hyperalgesia (defined as the presence of hyperalgesia, regardless of its degree).

To test the allodynic area around the surgical incision, each patient was assessed with the von Frey filament just below the one that evoked pain on the opposite side in the postoperative pain threshold test. Stimulation started far away from the surgical incision and moved towards the incision at 1 cm steps until the patient reported a distinct change in perception, from a touch sensation to a painful, sore or sharp feeling was marked, and the distance to the incision measured. The incidence and extension of the allodynic area were then calculated as described for the hyperalgesia area.

Pain evaluation at one and three months

Patients were contacted by telephone at one and three months after hospital discharge to collect data about postoperative pain. Patients measured pain intensity at one and three months using the numeric rating scale (NRS). A cut-off value of NRS >50 was then applied to identify severe and disabling pain as previously suggested.[18] To distinguish between non-neuropathic and neuropathic components of postoperative pain reported at one and three months, we used the PainDETECT Questionnaire (PD-Q), a validated, easy to use, patient-based (self-report) screening tool that quantifies to what extent neuropathic components contribute to chronic pain.[27 28] The PD-Q incorporates seven weighted sensory descriptor items (never to very strongly) and two items relating to the spatial (radiating) and temporal characteristics of the individual pain pattern: none of the items requires a clinical examination. The German PD-Q was translated into Italian by a professional translator; all of the patients received two copies of the questionnaire on hospital discharge.

Statistical analysis

Data were analysed using SPSS 15.0 package (SPSS Inc., Chicago, IL, USA). Results for normally distributed data for quantitative variables were expressed as mean [95% confidence interval (CI)] or median (inter-quartile range), and for qualitative variables as percentage. Student's *t*-test or Mann–Whitney *U*-test were used to assess differences for quantitative variables, and Pearson's χ^2

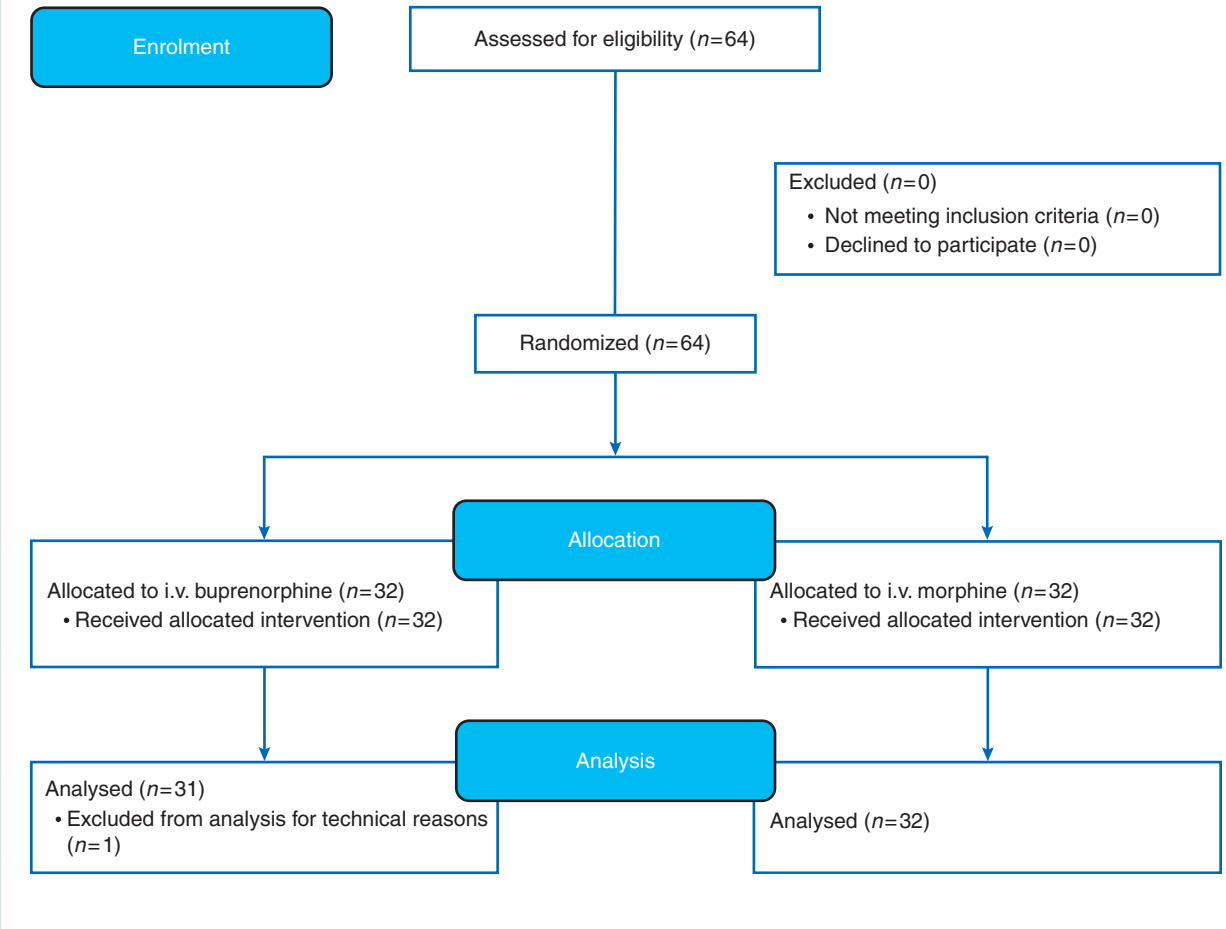

Fig 1 Flow diagram of the progress through the phases of trial.

test or Fisher's exact test were used to assess differences for qualitative variables.

Because the threshold values for the outcome variables assessed follow an exponential pattern, values for further analysis were log transformed. Preoperative collected data were considered as reference and used to normalize postoperative test results for individual patients by calculating the z-transform: z-score = (single value for each patient minus mean value for controls) divided by the standard deviation (SD) of controls.[29]

The time required for the first requested morphine rescue dose in the PACU in the first 30 postoperative minutes was evaluated by survival analysis (survival was equivalent to 'no morphine request'). Kaplan–Meier survival curves were constructed and the null hypothesis of no difference in survival among groups was tested with the log-rank test. The Cox proportional hazards model was used to calculate the hazard ratio with its relative 95% CI.

A P-value <0.05 was considered to indicate statistical significance.

Primary end-points were the presence and extent of the hyperalgesic area. From a pilot study conducted in the same setting, we hypothesized that patients treated with buprenorphine would have a 50% risk of a postoperative hyperalgesic area developing around the surgical incision (*vs* almost all of the patients receiving the control infusion). If hyperalgesia developed, we also hypothesized a 35% reduction in its extent *vs* controls (an expected difference in populations means of 26 cm^2 with an expected SD of 36 cm^2). A sample of 30 subjects per group would be sufficient to reject the null hypothesis that a hyperalgesic area would develop in a similar number of subjects in both groups, and have a similar mean extent, with 0.8 probability (power), and a 5% risk of type I error.[30] To account for possible dropouts, we planned to enrol 32 patients in each group.

Results

Patient characteristics

Of the 64 patients prospectively enrolled for this trial, 63 successfully completed the study (31 in the buprenorphine group and 32 in the control group); data for one patient were excluded from the analysis for technical reasons linked to poor nocturnal PCA management. Demographic characteristics of the studied population are shown in Table 1. No differences were found in the preoperative variables between groups or in the length of

Table 1 Demographic characteristics. Unless specified, all values are expressed as mean (95% CI). Type of surgery: 1, lobectomy; 2, sleeve resection; 3, atypical resection; 4, pneumectomy

	Groups		
Variables	Buprenorphine (n=31)	Morphine (n=32)	P-value between groups
Age (yr)	66 (63–69)	63 (60–66)	0.21
Height (cm)	167 (164–170)	166 (163–168)	0.74
Weight (kg)	70 (66–75)	72 (67–77)	0.63
Gender (% male)	55	53	0.89
ASA class I/II/III (n)	3/18/10	3/24/5	0.14
Type of surgery 1/2/3/4 (n)	18/3/10/0	14/2/14/2	0.34
Surgical incision (cm)	12 (11–14)	11 (10–12)	0.12
Duration of surgery (min)	108 (90–127)	109 (92–125)	0.97
Hospital stay (day)	7 (6–8)	7 (6–8)	0.64

hospital stay, and no postoperative complications of importance developed during the three month follow-up.

Postoperative analgesia

Mean time from extubation to first morphine rescue dose was twice as long in the group treated with buprenorphine than in patients receiving morphine (Fig. 2): 18 min (95% CI 14–23) *vs* 9 min (95% CI 6–12) (P=0.002 by log-rank test). Thirty minutes after surgery ended, the risk of receiving an analgesic rescue dose was higher in patients receiving morphine than in those receiving buprenorphine: hazard ratio 2.67 (1.27–5.64) (P=0.009 by Cox proportional hazard model). No significant difference was found in the total morphine titration dose required to discharge patients from the PACU between the two treated groups (P=0.08).

Although no difference was found in morphine PCA consumption between groups, buprenorphine induced a significantly larger reduction in postoperative VAS pain scores, both at rest and during coughing and at all time points, in the treated group than in the control group (P<0.05, Fig. 5).

Postoperative QST

Buprenorphine treatment significantly increased postoperative tactile and pain thresholds at 1 cm from the surgical incision (Table 2, Fig. 4). After buprenorphine infusion, but not after morphine infusion, postoperative tactile thresholds increased more on the operated side than on the contralateral side.

QST disclosed a distinct area of hyperalgesia around the surgical incision in more patients in the control group than in the treated group (87 *vs* 27%). The mean hyperalgesic area was significantly smaller in patients treated with low-dose buprenorphine infusion than in controls receiving morphine alone (Fig. 3). No difference was found in the extent of allodynic areas (Table 2). Of note, a small number of patients complained of allodynia in both groups without statistical significance.

Pain evaluation

The response rate to the postoperative telephone interviews was 60% at one month and 73% at three months. One month after surgery, fewer patients in the buprenorphine group than in the morphine group reported having severe, disabling pain (NRS >5) (16.7 *vs* 50%). At three months, the difference between groups disappeared (buprenorphine, 13.6%; morphine, 27.3%). No significant differences were found between groups in PD-Q scores or in the percentage of patients with a high or low probability of neuropathic pain (Table 2).

Discussion

In this double-blind, randomized, active-controlled trial, we provide new evidence showing that buprenorphine, infused at a low dose during general anaesthesia in patients undergoing major lung surgery, prevents peri-incisional postoperative hyperalgesia and reduces the hyperalgesic area. The risk of hyperalgesia developing was significantly lower in buprenorphine-treated patients than in the untreated controls (27 *vs* 87%).

Because surgically-induced primary and secondary hyperalgesia cannot be clinically distinguished from OIH, it is difficult to speculate on which of the two our patients' QST scores reflect. Although remifentanil is widely used owing to its rapid and predictable onset and offset, many studies describe hyperalgesic effects after remifentanil infusion even in healthy volunteers.[11 12 31 32] In patients undergoing remifentanil infusion, who often report receiving unsatisfactory analgesia, some investigators also describe acute drug tolerance and underline the need for greater postoperative analgesic doses.[5] It is difficult to discern, in clinical settings, to what extent either hyperalgesia or acute tolerance contribute to patients' reported pain and opioid consumption, thus we conjecture that in our patients and controls both these unwanted effects developed. Although the mechanisms underlying hyperalgesia and acute tolerance are still unknown, literature reports central nociceptive system activation through NMDA receptors.[33] Zhao and colleagues[8] have also shown that remifentanil induces an increased NMDA-mediated response through activation of σ receptors. Activation of μ and σ receptors, but not k, has been implicated as one of the mechanisms underlying development of OIH.[34] Activation of μ receptors by morphine increases cellular expression of σ receptors.[35] Moreover pharmacological inhibition and genetic mitigation of σ receptors increase μ-mediated spinal anti-nociceptive effects and inhibit tolerance in animals treated with morphine.[35] In an experimental study, Ddrla and colleagues[36] showed that opioid-induced hyperalgesia, namely opioid-withdrawal-related long-term potentiation at first C-fibre synapses, can be prevented by an NMDA-receptor antagonist

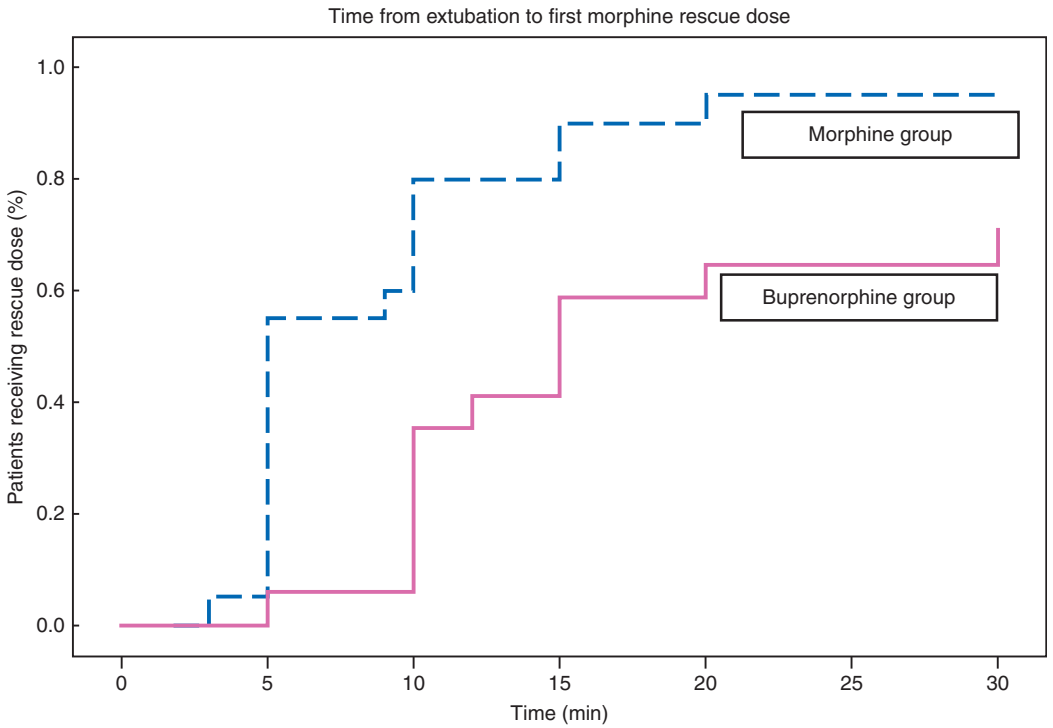

Fig 2 Kaplan–Meier plot showing how the mean time from extubation to first rescue dose was longer in the patients treated with buprenorphine than in those treated with morphine. At 30 min postoperatively the hazard ratio was 2.67 (1.27–5.64) (P=0.009 by Cox-proportional hazard model).

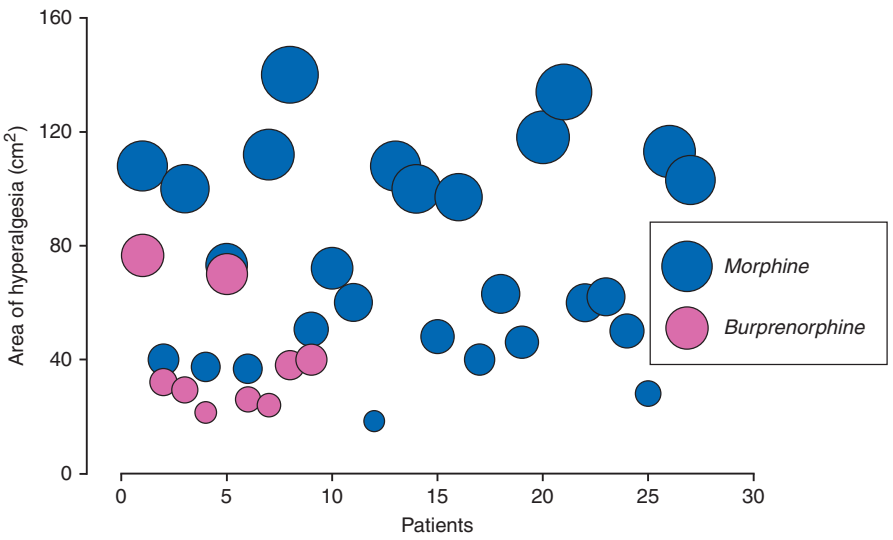

Fig 3 Bubble chart showing that fewer patients in the buprenorphine group developed an area of hyperalgesia (number of bubbles), and the mean extension of these areas was significantly smaller (dimension of bubbles). Each circle represents a single patient and his/her localization and measurement of peri-incisional mechanic hyperalgesic area. The size of each circle is proportional to the measured area.

Table 2 Postoperative analgesia, quantitative sensory testing (QST), and one and three month pain evaluation in the two groups. If not specified, all values are expressed as mean (95% CI). All P-values have been approximated to the second decimal. PACU, post-anaesthesia care unit; PCA, patient-controlled analgesia; PONV, postoperative nausea and vomiting; PD-Q, PainDETECT Questionnaire; NRS, numeric rating scale. A PD-Q score <18 indicates that a neuropathic pain component could be present

	Group		
Variables	Buprenorphine (n=31)	Morphine (n=32)	P-value between groups
Postoperative analgesia			
Morphine titration in the PACU (mg)	17 (12–21)	13 (10–17)	0.26
Total morphine PCA consumption (mg)	7 (4–10)	11 (8–14)	0.08
Time from extubation to first morphine (min)	18 (14–23)	9 (6–12)	0.01
PONV (%)	9.7	21.9	0.31
Postoperative QST			
z-values for tactile threshold changes	1.04 (0.57–1.50)	0.15 (−0.56–0.86)	0.04
z-values for pain threshold changes	0.53 (0.10–0.96)	−0.11 (−0.60–0.37)	0.04
Presence of area of hyperalgesia (%)	27	87	0.01
Extent of area of hyperalgesia (cm^2)	40 (21–59)	74 (59–88)	0.02
Extent of area of allodynia (cm^2)	49 (35–63)	71 (46–97)	0.32
One and three months pain evaluation			
PD-Q score at 1 month	7 (4–10)	10 (7–13)	0.15
PD-Q score at 3 months	7 (5–10)	8 (6–11)	0.60
PD-Q score <18 at 1 month (%)	17	33	0.44
PD-Q score <18 at 3 month (%)	9	32	0.13
Patients with severe pain (NRS >5) at 1 month (%)	16	50	0.05
Patients with severe pain (NRS >5) at 3 months (%)	14	27	0.46

without affecting acute synaptic opioid agonist depression. Convincing clinical and experimental evidence confirms that NMDA receptors have a key role in inducing and maintaining hyperalgesia.[11 12 32 37]

Postoperative hyperalgesia developed in both of our study groups; however, fewer patients complained of hyperalgesia, and the extent of the hyperalgesic area was significantly smaller in patients treated with buprenorphine (an opioid with NMDA-mediated anti-hyperalgesic properties) than in controls (Fig. 3).[38] No differences between groups were found in the dimension of allodynic areas (Table 2).

We cannot differentiate to what extent buprenorphine counteracted post-remifentanil OIH instead of surgically-induced hyperalgesia; it is possible that buprenorphine, through its anti-NMDA action, could have reduced both. In experimental models of acute and chronic pain in rats, buprenorphine significantly inhibits the development of mechanic and thermal allodynia and mechanic hyperalgesia.[17] Also, in experimental human models, buprenorphine significantly decreases hyperalgesic areas, and its anti-hyperalgesic effects seem to be more pronounced and last longer than those induced by other conventional analgesics.[13] A possible explanation for the buprenorphine anti-hyperalgesiac effect is its k-receptor antagonism which, through a dynorphin-mediated mechanism, may block pro-nociceptive NMDA-mediated activity.[13 14]

The reason why we measured hyperalgesic and allodynic areas with QST,[39] before and after surgery, and on the contralateral non-operated side, is that neither postoperative VAS nor opioid consumption correlate with the development of hyperalgesia. We measured the hyperalgesic area around the surgical incision by modifying a previously described method.[24–26] Our QST experimental protocol aimed to provide variables for assessing sensory loss (hypoesthesia) and sensory gain (hyperalgesia, allodynia, hyperpathia). Detailed sensory examinations can identify the mechanisms underlying postoperative pain processing. Contrasting results have been reported for the tactile threshold, increased or decreased, in the area around the wound or inflammation.[40 41] A strength of our study is that by comparing preoperative and postoperative tactile and painful thresholds we established the normal thresholds for each subject and measured possible changes. Because 'hyperalgesic' areas measured with a punctuate probe should be technically considered as areas of allodynia rather than of hyperalgesia,[39] each patient was tested with the von Frey filament that evoked pain in the postoperative test for pain threshold on the opposite side. According to the International Association for the Study of Pain (IASP) definitions of hyperalgesia and allodynia, whether stimuli are normally painful or normally non-painful determines the difference between them. In buprenorphine-treated patients, QST showed significantly increased tactile and pain thresholds. The statistical z-value compares tactile and pain thresholds for each patient with those for controls. Values close to 0 indicate no difference with controls, significantly positive values indicate the thresholds are higher than those in controls (gain of function), whereas significantly negative values signal loss of function (Fig. 4). When we assessed the tactile and pain thresholds on the contralateral non-operated side, we found them higher than those in controls. This finding suggests that buprenorphine probably induces its anti-hyperalgesic action through a central mechanism: on the operated side, buprenorphine increased pain thresholds and reduced hyperalgesia; on the contralateral non-operated side, buprenorphine increased tactile thresholds. The combined sensory loss, pain and lowered pain detection thresholds to different stimuli is a phenotype characteristic for neuropathic pain.[40]

Thoracotomy is, along with limb amputation, considered to be the surgical procedure that elicits the highest risk of severe

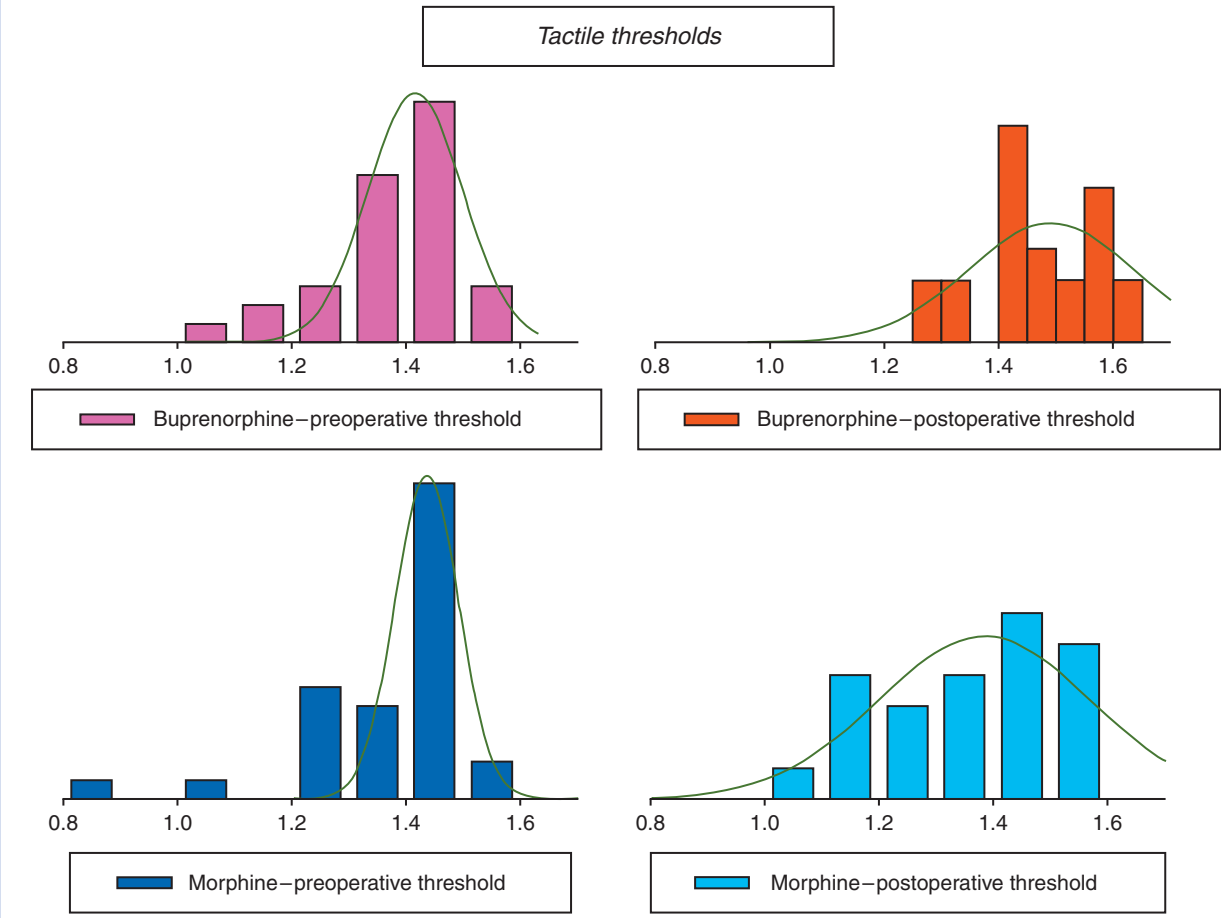

Fig 4 Bar histograms showing increased postoperative tactile threshold 1 cm from the surgical incision in the buprenorphine group with respect to control. Normalized and log-transformed values for tactile thresholds (x-axis); number of patients (y-axis).

chronic postoperative pain,[18] half of which definitely or possibly includes a neuropathic component.[28] Although we could not detect hypoesthesia owing to persistent primary and secondary hyperalgesia around the surgical site, buprenorphine's anti-hyperalgesic action may explain why we found increased tactile and pain thresholds in the treated patients. Why buprenorphine infusion significantly increased the tactile threshold on the operated side compared with the contralateral side whereas morphine infusion did not, remains unclear.

In a recent exhaustive review on postoperative OIH, Fletcher and Martinez[6] reported a 24 h increase in postoperative pain, a moderate increase in morphine use, with no impact on opioid-related side effects, attributed to remifentamil-induced hyperalgesia. In our study, we showed that, although the total morphine titration dose required to discharge patients from the PACU did not significantly differ between treated groups, patients treated with buprenorphine had reduced postoperative pain scores, both at rest and during coughing, during their PACU stay (Fig. 5). We also found that the time elapsing between extubation and the first morphine rescue dose was twice as long in buprenorphine-treated patients than in the controls (Fig. 2).

Although the patients treated with buprenorphine experienced markedly less severe pain than controls one month postoperatively, this difference disappeared at three months. This result suggests that buprenorphine counteracts persistent postoperative pain, leaving the risk of developing chronic pain unchanged; definitive conclusions await a larger study with the same setting and methodology.

Our study has several limitations. First, being beyond the scope of our study, we decided not to analyse all possible QST variables (pressure, thermal and vibration thresholds) to reduce the duration (and potential discomfort) of the testing phase. Although the QST results in our study almost match the reference values published by the German Research Network on Neuropathic Pain,[29] we cannot compare the two directly because, at the time of analysis, they examined the hip rather than the chest, the studied population was younger and their testing algorithm differed from ours. Second, our modified protocol to measure postoperative hyperalgesia has some limits worth mentioning, namely the choice of von Frey filaments as testing probes and the potential bias of intra-subject side differences in the threshold value measurements. Thick von Frey filaments not only stimulate

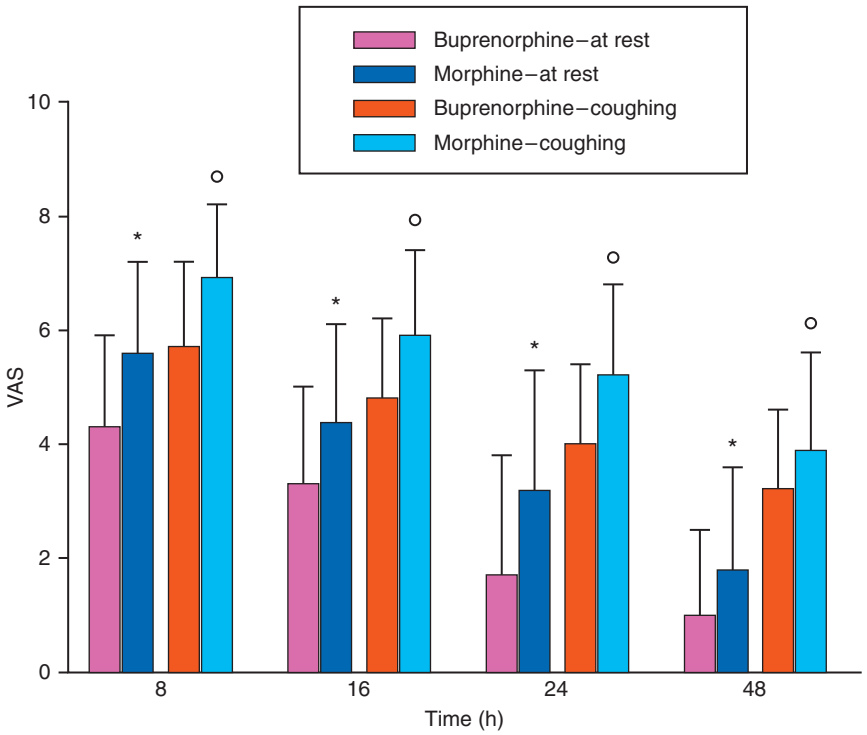

Fig 5 The 48 h postoperative pain was significantly lower in the treated group compared to the control group both at rest and during coughing (*$P<0.05$ at rest, °$P<0.05$ during coughing). VAS, visual analogue scale.

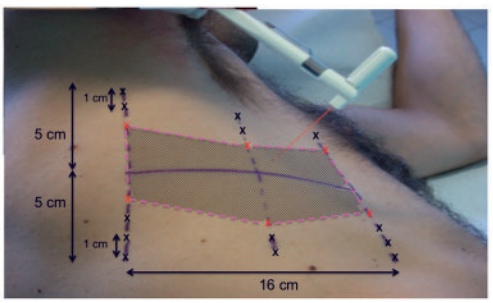

Fig 6 Diagram showing the technique used to define hyperalgesic and allodynic areas. Identified polygonal areas were divided in smaller polygons to simplify calculation.

low-threshold Aβ fibres, but also Aδ-fibre nociceptors (because the filament has sharp edges) or even C-fibre nociceptors (usually in patients with peripheral sensitization).[42] Because currently available bedside techniques cannot stimulate Aβ, Aδ or C-fibre afferents selectively,[39] experiments using von Frey filaments to quantify punctuate hyperalgesia cannot determine to what extent these different pathophysiology mechanisms are involved. Also, we did not take into account any potential threshold differences between the surgical and contralateral sides during the postoperative testing session, and we have always used the contralateral side to define 'normal' threshold values. The German PD-Q questionnaire, although professionally translated into Italian, it was not yet validated in Italy at time of administration, so its ability to discriminate a neuropathic pain component in a population of Italian subjects was still unknown. Last, the multimodal analgesic regimen might have interfered with acute opioid tolerance.[31]

In conclusion, a perioperative low-dose infusion of buprenorphine given to patients undergoing major thoracic surgery under remifentanil infusion is effective in preventing or reducing postoperative hyperalgesia. The drug reduces postoperative pain in the acute setting but it is not effective in preventing development of chronic postoperative pain.

Authors' contribution

Study design, data analysis and interpretation, first draft, revision, final draft and approval, agreed to be accountable for all aspects of the work: S.P.

Study design, draft, data analysis, final approval, agreed to be accountable for all aspects of the work: R.A.

Study design, data analysis, revision, final draft, final approval, agreed to be accountable for all aspects of the work: R.D.B., M.R.

Surgical protocol, study design, first draft, revision, final approval, agreed to be accountable for all aspects of the work: A.D.A.

Study design, patients' assessment, data analysis, first draft, revision, final approval, agreed to be accountable for all aspects of the work: A.N., S.T.

Anaesthesia protocol, study design, data collection and analysis, first draft, revision, agreed to be accountable for all aspects of the work: B.S., D.M.

Study design, data analysis and interpretation, supervision, first draft, revision, final draft and approval of the paper, agreed to be accountable for all aspects of the work: M.M.

Declaration of interest

None declared.

Funding

All costs were met by internal department funds.

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Handling editor: Lesley Colvin