British Journal of Anaesthesia **112** (6): 991–1004 (2014)
doi:10.1093/bja/aeu137

BJA

Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis

D. Fletcher[1,2,3]* and V. Martinez[1,2,3]

[1] Service d'anesthésie, Hôpital Raymond Poincaré, Garches, Assistance Publique Hôpitaux de Paris, Garches F-92380, France
[2] INSERM, U-987, Hôpital Ambroise Paré, Centre d'Evaluation et de Traitement de la Douleur, Garches F-92100, France
[3] Université Versailles Saint-Quentin, Garches F-78035, France

* Corresponding author. E-mail: dominique.fletcher@rpc.aphp.fr

Editor's key points

- Opioid-induced hyperalgesia (OIH) may occur with a paradoxical increase in pain after opioid administration.
- This systematic review and meta-analysis summarizes evidence from randomized, controlled trials for acute OIH.
- An increase in postoperative pain was associated with high-dose intra-operative opioid use.
- Further studies of different opioids are needed to explore the clinical implications of OIH.

Background. Opioids can increase sensitivity to noxious stimuli and cause opioid-induced hyperalgesia. We performed a systematic review to evaluate the clinical consequences of intra-operative doses of opioid.

Methods. We identified randomized controlled trials which compared intra-operative opioid to lower doses or placebo in adult patients undergoing surgery from MEDLINE, EMBASE, LILAC, Cochrane, and hand searches of trial registries. We pooled data of postoperative pain intensity, morphine consumption, incidence of opioid-related side-effects, primary and secondary hyperalgesia. For dichotomous outcomes relative risks [95% confidence intervals (CIs)] and for continuous outcomes mean differences (MDs) or standardized mean difference (SMD; 95% CI) were calculated.

Results. Twenty-seven studies involving 1494 patients were included in the analysis. Patients treated with high intra-operative doses of opioid reported higher postoperative pain intensity than the reference groups (MD: 9.4 cm; 95% CI: 4.4, 14.5) at 1 h, (MD: 7.1 cm; 95% CI: 2.8, 11.3) at 4 h, and (MD: 3 cm; 95% CI: 0.4, 5.6) at 24 h on a 100 cm visual analogue scale. They also showed higher postoperative morphine use after 24 h (SMD: 0.7; 95% CI: 0.37, 1.02). There was no difference in the incidences of nausea, vomiting, and drowsiness. These results were mainly associated with the use of remifentanil. The impact of other opioids is less clear because of limited data.

Discussion. This review suggests that high intra-operative doses of remifentanil are associated with small but significant increases in acute pain after surgery.

Keywords: mechanism, meta analysis; pain; postoperative, analgesics opioid, analgesics opioid; remifentanil, pain

Accepted for publication: 22 January 2014

Opioid-induced hyperalgesia (OIH) has been clearly demonstrated in animal models[1] and in human volunteers.[2] The opioids identified as potentially causing OIH in these experimental conditions are remifentanil, fentanyl, morphine, and diamorphine.[2–4] In patients after surgery, OIH and tolerance have been studied mainly after opioid-based anaesthesia[5–21] and also during postoperative analgesia.[22–24] These results were used to highlight a pathophysiological phenomenon, but the real clinical impact of OIH has never been estimated, because of lack of sufficient data and conflicting results. Since previous reviews of this topic,[25–27] many studies assessing the OIH after surgery have been published. In addition, all the studies of OIH have used small population sizes, so inflating their risk of Type II statistical error. Therefore, the aim of this systematic review and meta-analysis was to determine whether OIH has a clinical impact on patient's perception of pain after surgery.

The aim of this systematic review was to quantify the clinical impact of intra-operative OIH in patients after surgery. We chose acute pain intensity at rest 24 h after surgery as the primary outcome measure. Secondary outcome measures were 24-h morphine use, pain intensity on movement, postoperative opioid use, incidence of postoperative opioid-related side-effects, and hyperalgesia measured after operation.

Methods

This systematic review of randomized, controlled trials (RCTs) was performed according to the criteria of the PRISMA statement and the current recommendations of the Cochrane Collaboration.[28 29] The protocol was registered with PROSPERO under the number CRD42013004846.

Search strategy and study selection

We attempted to identify all relevant studies regardless of language or publication status (published, unpublished). We searched for RCTs indexed in the following databases: Cochrane Central Register of Controlled Trials, CENTRAL, PUBMED, EMBASE, and LILACS. We applied the highly sensitive search strategy of the Cochrane collaboration to identify randomized trials.[30] The search strategy combined free text words and controlled vocabulary MeSH terms with no limitation on the period of research. The search equation for PUBMED was adapted for each database (Supplementary Appendix). The last search was performed in June 2013. We also searched the proceedings of the two major annual meetings of anaesthesiology societies (ASA, ESA) in the last 5 yr. We searched for RCTs in the meta-Register of Controlled Trials (clinicaltrials.gov). Both authors independently screened titles, abstracts, and full texts according to the inclusion criteria. All instances of discordance were discussed between the investigators to reach a consensus. The reasons for exclusion of each publication were recorded.

Population

Populations included were: (i) adults and children, (ii) undergoing surgery, and (iii) receiving opioid for anaesthesia.

Outcomes

The primary outcome was pain at rest at 24 h expressed on a visual analogue scale (VAS: 0: no pain to 100: worst possible pain). Intensity scores reported on a numerical rate scale (NRS: 0: no pain to 10: worst possible pain) were transformed to a 0-to-100 VAS scale. The following outcomes were considered as secondary outcomes: cumulative morphine consumption over the 24 h postoperative period expressed in milligrams of morphine equivalent, morphine titration in the post anaesthesia care unit (PACU); pain at rest at other time points (1 h, 4 h), pain on movement; secondary hyperalgesia defined by the area of mechanical allodynia around the wound; primary hyperalgesia defined as the mechanical pain threshold close to the wound; and number of patients with opioid-related adverse events at 24 h [nausea, vomiting, the combination of postoperative nausea and vomiting (PONV), drowsiness].

Intervention

Interventions included were remifentanil, sufentanil, or fentanyl administered during the surgical procedure, whatever the timing, the dose, or the mode of administration. The comparator arm was a lower dose of the same opioid or a placebo. The study exclusion criteria were: (i) analgesia techniques or medication not being equivalent or comparable between groups during the intervention and (ii) the duration of the study limited to the stay in the PACU.

Quality assessment

The Cochrane collaboration's tool for assessing risk of bias was used to evaluate the risk of bias in the randomized, controlled studies selected. The following risks of bias domains were assessed: generation of the allocation sequence, allocation concealment, blinding of investigators and participants, blinding of outcome assessors, incomplete outcome data. Each item was classified as low, unclear, or high risk of bias.

Data extraction

Data were extracted by the two authors using a standardized extraction procedure. We extracted information on studies' general characteristics (including design, number of arms, and primary outcomes), participants (characteristics of the populations, sample size, and type of surgery), and experimental intervention (type of opioid, doses, and administration mode).

Dichotomous outcomes were extracted as the presence or absence of an effect. For continuous data, we extracted means and standard deviations (SDs). If not reported, the SDs were obtained from confidence intervals or *P*-values that related to the differences between means in the two groups.[30 31] If medians with range were reported, mean and SD were obtained with the formulae reported by Hozo and colleagues.[32] If treatment and control effect size were not reported in the text, but in graphical representations, data values were extracted from the graphs using dedicated software (ref: http://www.datathief.org/). We contacted authors by e-mail to obtain missing data and for further details about the study results. In cases of non-response, a second e-mail was sent. When results of eligible trials were available in abstracts only, we contacted the authors to ask for a report of the trial results.

Data synthesis and analysis

For studies in which more than two groups with different doses of intraoperative opioid were compared, we used the group with the lowest dose as the control group. Pain scores reported within 1 h of our time points were included in the analysis. Pain intensity scores were assumed to be at rest unless otherwise noted. Doses of opioids other than morphine were converted to morphine equivalents using standard conversion factors (i.e. 0.1 for i.v. meperidine, 0.75 for i.v. piritramide,[33] 1.33 for i.v. oxycodone,[34] 5 for i.v. hydromorphone[34] and 100 for fentanyl).[35] Nausea, vomiting and nausea, and vomiting were analysed separately.

We computed risk ratios (RRs) with 95% CI for dichotomous data and calculated the mean differences with 95% CI for continuous data. Morphine consumption at 24 h was reported with different value scales in different studies (mg 24 h^{-1}, mg kg^{-1} 24 h^{-1} or mg h^{-1}), we expressed treatment effects for the morphine consumption as standardized mean difference (SMD) by dividing the difference in mean values between treatment groups by the pooled SD. An SMD of 0.2 indicates small differences between groups whereas 0.5 suggests moderate and 0.80 large differences.[36] To interpret the clinical significance of SMD, we can calculate the mean difference (MD) of morphine use for 24 h with the following formula: MD=SMD $\times$ median SD. The SD was calculated from the SD of each surgical model in all included studies according to a

previous publication.[37] The estimation of this median SD was 27 mg.

We expected heterogeneity (because of the diverse populations included) and therefore used Dersimonian and Lairs random effects meta-analysis modules. We assessed heterogeneity with the I^2 statistic ($I^2>50\%$ indicates substantial heterogeneity). Investigation of sources of heterogeneity was based on analysis of pre-specified subgroups. The definition of the subgroups included: type of opioid, type of anaesthesia; type of comparison; and global risk of biases. Finally, we tested for funnel plot asymmetry using the Egger test and drew contour-enhanced Funnel plots to address reporting biases. All statistical analyses were performed with the Review Manager (RevMan version 5.2.5; The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). R software was used for funnel plots and Egger tests.

Results

Search results

The systematic literature search identified 703 relevant publications. After review of titles and abstracts, 37 studies were selected as being potentially eligible for inclusion into this systematic review. After reading the full-text articles, 27 RCTs (published between 1994 and 2013) including 1494 participants were finally included (Fig. 1) . No unpublished trials were identified with our eligibility criteria in the clinicaltrial.gov register. One trial published as an abstract and for which unpublished results were provided by the author was included in the analysis.[38] Following our requests for additional information to obtain missing values, three authors provided additional data.[15 38 39]

Trial, participants, and intervention characteristics (Table 1)

All the studies involved single sites. The median target sample size was 50 (18–200) [median (min–max)] patients. Participants were adults or children with ASA physical status classes I to III. The studies investigated patients undergoing surgery in different specialties: gynaecology,[7 10 17 40–42] abdominal surgery,[9 11 39 43] Caesarean section,[6 44 45] cardiac surgery,[44 45] orthopaedic surgery,[38 46 47] urology,[48 49] tonsillectomy,[49] and thyroidectomy.[50] General anaesthesia was maintained with inhalation anaesthetic agent(s)[7 9–11 18 40–43 48–53] or with an infusion of propofol.[15 18 20 21 38 39 46 47] Spinal anaesthesia was performed in four trials.[6 17 45 44] The majority of RCTs ($n=19$) investigated OIH in patients treated with remifentanil.[9–11 15 18 20 38–41 43 46–54] Three RCTs explored i.v. fentanyl,[7 17 42] one sufentanil,[21] and four intrathecal fentanyl.[6 21 44 45] The comparator(s) in most studies were a low dose of the experimental opioid ($n=15$);[7 9–11 18 20 21 38 39 41 48 49 52 53] placebo was used in nine trials;[6 15 17 42 43 45–47 54] and both comparators were used in three trials.[39 40 44 51] The remifentanil administration scheme differed between the trials included. Most used a combination of a remifentanil bolus followed by a continuous infusion, which varied from 0.05 to 0.9 $\mu g\ kg^{-1}\ min^{-1}$. The mean duration of anaesthesia was between 54 and 324 min. This leads to a mean cumulative dose of remifentanil from 381 to 5644 μg [overall mean of 2297 (1890)]. Two RCTs reported outcome values in format unusable for meta-analysis.[6 43] Twenty-five RCTs were therefore included in the meta-analysis (Table 1).

Risk of bias assessment of included studies (Figure 2)

Fifteen trials were classified as being at low risk of bias, 11 at unclear bias, and 1 at high risk. The randomization procedure was adequately described in 17 (67%) and concealment of treatment allocation was described in six (22.2%). Ten studies (37%) were double-blinded; all others were classified as unclear. Four studies had an unclear or high risk of incomplete data outcomes (Fig. 2). The registered protocols were retrieved for three trials,[15 50 51] all three of which were at low risk of bias for selective reporting.

Pain intensity

Seventeen trials including 863 patients compared postoperative pain intensity at rest at 24 h, 11 trials including 469 patients at 4 h, and 12 trials including 660 patients at 1 h. At all time points, the experimental groups reported significantly higher pain scores at rest than the control groups; the mean difference in pain was greater early in the postoperative period (1, 4 h) than at 24 h (Fig. 3). However, these pooled data analyses for the 1, 4, and 24 h postoperative time points were influenced by heterogeneity (Fig. 3). Eight trials including 388 patients compared postoperative pain intensity on movement at 24 h. There was no significant difference in the increase in pain on movement between the experimental and reference groups [1.48 (−0.77, 3.54), $P=0.2$, $I^2=0\%$].

Postoperative morphine use

Five RCTs including 276 patients reported data on morphine titration in PACU[11 15 20 39 40] and 14 RCTs including 816 patients reported data on 24 h cumulative morphine use.[9 10 15 17 18 38–41 44 46–49 51–53] More morphine was required by patients who had received intraoperative opioid than controls (Fig. 4). However, the results were influenced by heterogeneity. The estimation of the 24 h morphine use mean difference was 18 mg.

Primary and secondary hyperalgesia

Five trials including 471 patients explored primary hyperalgesia. The reported pain thresholds were significantly lower for the experimental group than the control group (Fig. 5). Four trials including 181 patients explored secondary hyperalgesia. A slight trend was found for a larger area of secondary hyperalgesia in the experimental group, but the SMD was not significantly different to that for the controls (Fig. 5). However, visual inspection and subgroup analysis focusing on type of opioid showed contrasting results for remifentanil trials[11 20 41 50 52] and for sufentanil[21] and fentanyl[42] trials (Fig. 5). In the remifentanil subgroup, SMD for both primary hyperalgesia and secondary hyperalgesia were substantially different (Fig. 5).

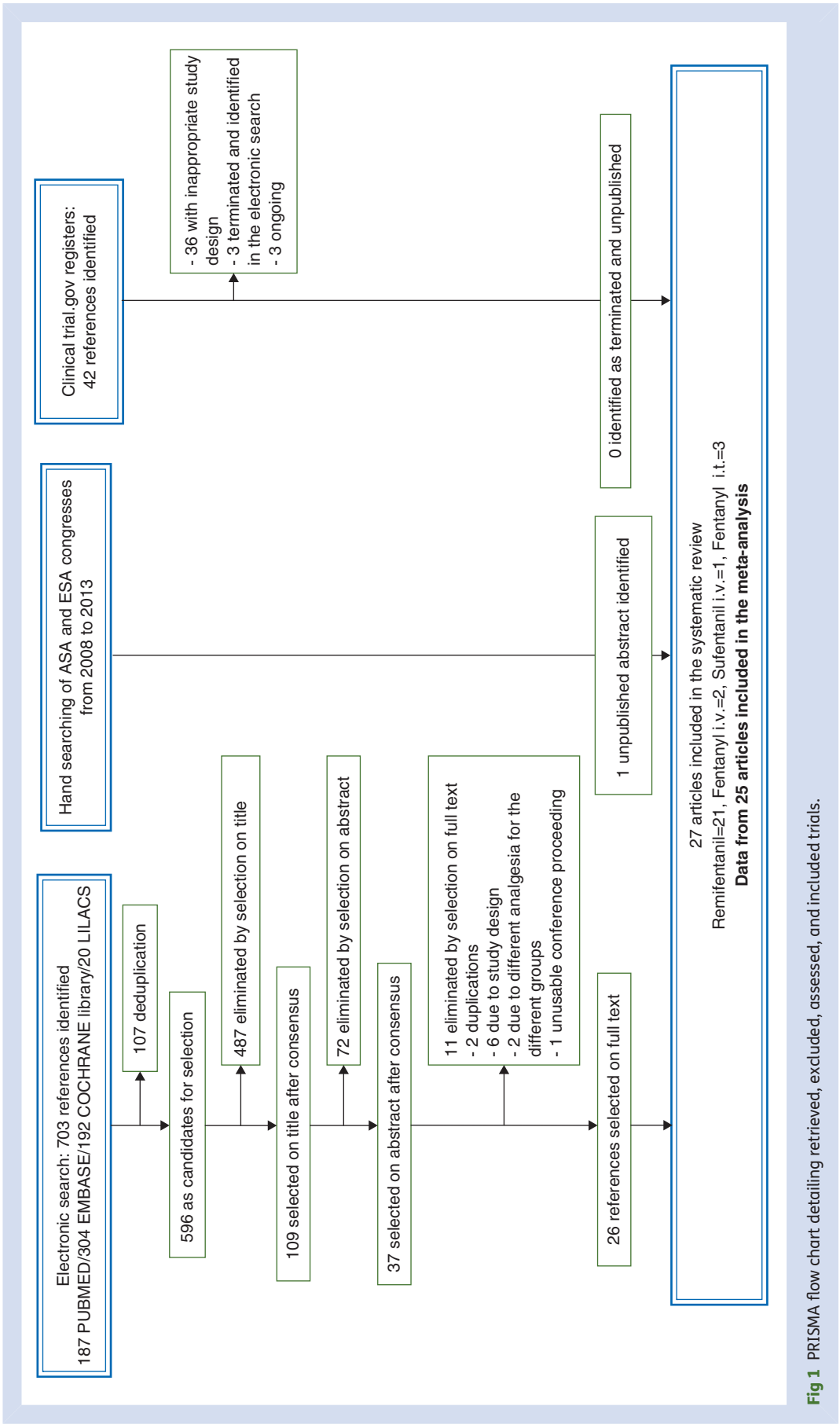

Fig 1 PRISMA flow chart detailing retrieved, excluded, assessed, and included trials.

Table 1 Characteristics of included studies. TCI, target controlled infusion; VAS, visual analogue scale; NRS, numerical rating scale; PONV, postoperative nausea and vomiting; PON, postoperative nausea; POV, postoperative vomiting; PCA, patient-controlled analgesia; PACU, post-anaesthesia care unit

Study (first author, year)	Number of patients in control or low opioid dose group	Number of patients in high opioid dose group	Patients/surgery	Intervention	Outcomes
Agata[53] (2010)	15 low dose	15	Elective orthognatic surgery	I.V. remifentanil (0.15 μg kg min^{-1}) *vs* (> 0.3 μg kg min^{-1})	Pain VAS at rest at 1, 3, 6, 12 and 24 h. PCA i.v. fentanyl 24 h. Haemodynamic variables 12 h. PONV and shivering 24 h
Carvalho[44] (2012)	9 control 9 low dose	9	Caesarean section	Intrathecal single shot fentanyl (5 μg) *vs* (25 μg)	Pain VAS at rest, oxygen saturation and respiratory rate 30 min, 1, 4, 8, 12 and 24 h. Intraoperative pain, nausea, hypotension, and vasopressor use. PCA i.v. morphine 24 h
Chia[7] (1999)	30 low dose	30	Hysterectomy	1 μg kg^{-1} fentanyl bolus *vs* 15 μg kg^{-1} bolus plus 100 μg h^{-1} infusion	Pain VAS at rest 4, 8, 12, and 16 h. Haemodynamic, arterial blood gas, and sedation scores. PCA i.v. morphine 24 h
Cho[40] (2008)	30 control 30 low dose	30	Gynaecology	I.V. remifentanil (target 1 ng ml^{-1}) *vs* high-dose remifentanil (target 3 ng ml^{-1})	Pain VAS at rest 15, 30, 45, 60 min and 6, 12, 24, and 48 h. Sedation, agitation. PCA i.v. morphine 48 h. PONV requiring antiemetic
Cooper[6] (1997)	30 control	30	Caesarean section	Intrathecal single shot fentanyl (25 μg) *vs* placebo	Intraoperative most severe pain; intraoperative nausea, vomiting, drowsiness. Pain VAS at rest and during coughing at 15 min, 3, 6, 10, and 23 h. PON, POV, pruritus, drowsiness. PCA i.v. morphine 24 h
Cooper[45] (2002)	18 control	18	Caesarean section	Intrathecal single shot fentanyl (25 μg) *vs* placebo	Pain VAS at rest and during coughing in PACU and then at 2, 4, 10, and 20 h. Intraoperative pain; PON, POV, pruritus, drowsiness. PCA epidural fentanyl
Cortinez[10] (2001)	30 control	30	Gynaecology	I.V. remifentanil (0.23 μg kg min^{-1}) *vs* placebo	Pain VAS during coughing at 15, 30, 45, 90 min, 2, and 24 h. PCA i.v. morphine 24 h, PONV, sedation, hypoxemia (pulse oximeter), respiratory depression; patient satisfaction
Fechner[21] (2013)	18 low dose	16	Coronary artery bypass graft	I.V. sufentanil (target 0.4 ng ml^{-1}) *vs* remifentanil (target 0.8 ng ml^{-1})	Pain NRS at rest and during deep inspiration, PCA i.v. morphine 48 h. Cognitive function, sedation, constipation, PONV. Primary and secondary hyperalgesia
Guignard[9] (2000)	25 low dose	24	Colorectal surgery	I.V. remifentanil (0.1 μg kg min^{-1}) *vs* (0.3 μg kg min^{-1})	Pain VAS at rest at 24 h. PCA i.v. morphine 48 h. PON, POV, pruritus, dysphoria, diplopia, hallucinations
Hansen[43] (2005)	18 control	21	Major abdominal surgery	I.V. remifentanil (0.4 μg kg min^{-1}) *vs* placebo	Summed pain VAS at rest and during coughing at 4, 6, and 24 h. PCA i.v. morphine 24 h. PON, POV, sedation
Joly[11] (2005)	25 low dose	25	Major abdominal surgery	I.V. remifentanil (0.05 μg kg min^{-1}) *vs* (0.4 μg kg min^{-1})	Pain verbal scale for 3 h then pain VAS at rest every 4 h for 44 h. Pain VAS when peak flow measurement at 24 and 48 h. PCA i.v. morphine 48 h. PONV, laryngospasm, bronchospasm, respiratory depression, muscular rigidity, agitation, and shivering Primary and secondary hyperalgesia
Kim[51] (2013)	15 control 15 low dose	15	Paediatric urology	I.V. remifentanil (0.9 μg kg min^{-1}) *vs* (0.3 μg kg min^{-1})	Pain CHEOPS scale at rest. Parent–nurse controlled i.v. fentanyl analgesia. POV, drowsiness, pruritus
Lahtinen[15] (2008)	45 control	45	Cardiac surgery	I.V. remifentanil (0.3 μg kg min^{-1}) *vs* placebo	Pain VAS at rest and during deep breath every 8 h during 48 h. PCA i.v. oxycodone 48 h. PON, POV, sedation

Continued

Table 1 *Continued*

Study (first author, year)	Number of patients in control or low opioid dose group	Number of patients in high opioid dose group	Patients/surgery	Intervention	Outcomes
Lee (2011a)	30 control	30	Tonsillectomy	I.V. remifentanil (0.3 μg kg min^{-1}) *vs* placebo	Pain VAS during swallowing at 30 min, 1, 6, 12, and 24 h. Meperidine 24 h. Hypotension, postoperative haemorrhage, desaturation, prolonged hospitalization, readmission, for pain
Lee (2011b)	25 control	25	Prostatectomy	I.V. remifentanil (0.3 μg kg min^{-1}) *vs* placebo	Pain VAS at rest at 30 min, 6, 12, 24, and 36 h. PCA i.v. morphine 36 h. PON, shivering
Lee (2013a)	28 low dose	29	Hysterectomy	I.V. remifentanil (0.05 μg kg min^{-1}) *vs* high-dose remifentanil (0.3 μg kg min^{-1})	Pain VAS at rest at 1, 6, 12 and 24 h. PCA i.v. morphine 24 h. PONV, shivering Primary hyperalgesia
Lee (2013b)	30 low dose	29	Urologic surgery	I.V. remifentanil (0.05 μg kg min^{-1}) *vs* (0.3 μg kg min^{-1})	Pain VAS during movement at 1, 6, 12, and 24 h. PCA i.v. morphine 24 h. PONV, somnolence, dizziness Primary and hyperalgesia
Richebe[20] (2011)	19 low dose	19	Cardiac surgery	I.V. remifentanil (TCI 7 ng ml^{-1}) l (0.3 μg kg min^{-1})	Pain VAS at rest and during coughing every 4 h for 44 h. PCA i.v. morphine 44 h. Nausea, vomiting, pruritus, dysphoria, and sedation Primary and hyperalgesia
Ryu[54] (2007)	30 control	30	Gastrectomy	I.V. remifentanil (1 ng ml^{-1}) *vs* placebo	Pain VAS at rest at 15, 30, 45 min, 6, 12, 18, 24, and 30 h. No morphine; postoperative epidural analgesia
Sahin[46] (2004)	14 control	16	Lumbar discectomy	I.V. remifentanil (0.1 μg kg min^{-1}) *vs* placebo	PCA i.v. morphine 24h. Pain VAS PACU 1 h. PONV
Shin[18] (2010)	98 low dose	88	Breast cancer surgery	I.V. sufentanil (target 1 ng ml^{-1}) *vs* remifentanil (4 ng ml^{-1})	Pain VAS at rest at 30, 1, 6, 12, 24 h. PCA i.v. morphine 24 h. PONV
Song[50] (2011)	28 low dose	28	Thyroidectomy	I.V. remifentanil (0.05 μg kg min^{-1}) *vs* remifentanil (0.2 μg kg min^{-1})	Pain NRS at rest PACU, 6, 24, and 48 h. Tramadol and acetaminophen. PONV, dizziness, headache, shivering Primary hyperalgesia
Terao[38] (2010)	13 low dose	13	Elective wrist arthrodesis	I.V. remifentanil (0.1 μg kg min^{-1}) *vs* (0.8 μg kg min^{-1})	Pain NRS at rest PACU, 1, 2, 4, 6,12, 18, 24 h. PCA i.v. fentanyl 24 h
Tirault[39] (2006)	30 low dose	27	Major abdominal surgery	I.V. sufentanil (target 3 ng ml^{-1}) *vs* (8 ng ml^{-1})	Pain VAS at rest, sedation, PON, POV, pruritus, hallucinations, in PACU then every 4 h for 20 h. PCA i.v. morphine 24 h
Tverskoy[42] (1994)	9 control	9	Hysterectomy	Fentanyl bolus (5 μg kg^{-1}) then infusion (0.02 μg kg min^{-1}) *vs* placebo	Pain VAS at rest and during movement 24 and 48 h. Meperidine i.v. and i.m. Primary hyperalgesia
Xuerong[17] (2008)	15 control	15	Hysterectomy	Three fentanyl boluses of 1 μg kg^{-1} *vs* placebo	Pain VAS at rest 1, 3, 6, 12, 14, and 48 h. PCA i.v. morphine 48 h. PONV
Yeom[47] (2011)	20 control	20	Spinal fusion	I.V. remifentanil (0.03 μg kg min^{-1}) *vs* placebo	Pain NRS at rest 1, 24 and 48 h. PCA i.v. fentanyl. PONV

Opioid-related adverse events

The numbers of patients with nausea, vomiting, combined nausea and vomiting, and drowsiness in the postoperative period were reported in 5, 5, 12, and 5 trials, respectively. No significant differences were found for any of these measures (Table 2).

Heterogeneity, subgroup analysis, and reporting bias

For the primary outcomes, the I^2 statistic was 82% for morphine consumption and 55% for pain at rest at 24 h, showing high heterogeneity. Several characteristics of studies can lead to such heterogeneity and we explored four of them by subgroup analysis (type of opioid, type of anaesthesia, type of comparison, duration of anaesthesia) (Table 3). Analysis of the influence of different opioids clearly established that remifentanil was associated with higher MD of pain and SMD of morphine consumption at 24 h. The data available for i.v. and intrathecal fentanyl were sparse and inconsistent. However, the remifentanil subgroup was also influenced by heterogeneity. The influence of different methods of administration of anaesthesia revealed a higher SMD in morphine consumption

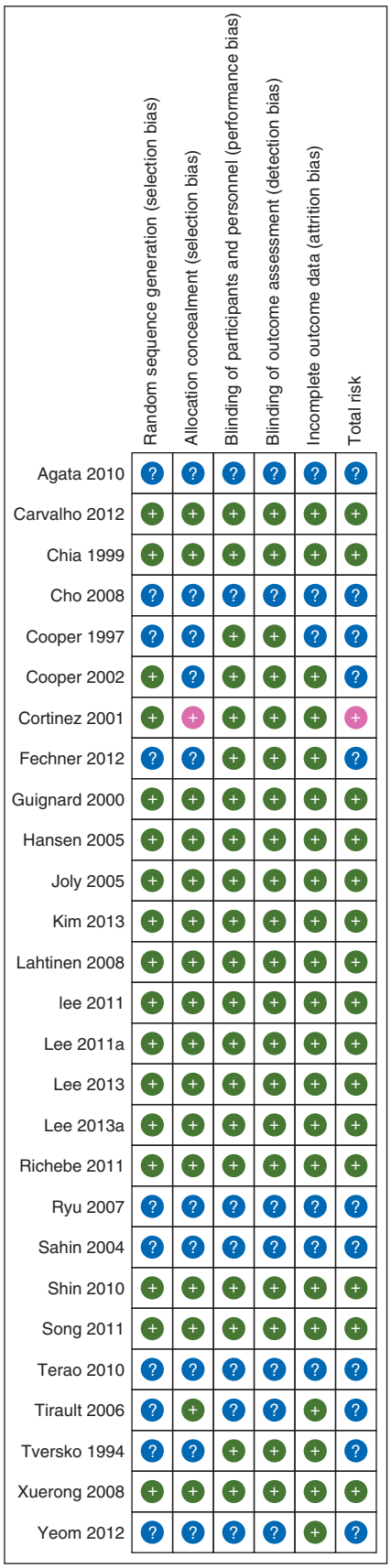

Fig 2 Forest plot for pain scores at rest at 1, 4 and 24 h. Pooled data analysis of the pain at rest in adults receiving intraoperative opioid vs control. CI, confidence interval.

for inhalation anaesthetic agents, and no difference for propofol anaesthesia. The observed homogeneity of the propofol group and the heterogeneity of this subgroup analysis provide strong support for the validity of the results. The MD in pain at rest was greater where low-dose groups were used for comparison than where placebo was used for comparison. The available data on the cumulative dose of remifentanil was insufficient to allow exploration of the influence of the dose. However, the infusion rate of remifentanil in the experimental group was higher in trials comparing the high and low doses [0.32 (0.22) $\mu g\,kg^{-1}\,min^{-1}$] than in trials comparing remifentanil and placebo [0.18 (0.12) $\mu g\,kg^{-1}\,min^{-1}$]. The influence of anaesthesia duration was also explored (classified as shorter or longer than 180 min) but did not reveal any differences (data not shown).

The sensitivity analysis of trial quality showed that the SMD of 24 h morphine consumption was higher in trials at low risk of biases [0.96 (0.49–1.43), $P<0.0001$] than in trials with unclear or high risks of biases [0.37 (−0.07–0.69), $P=0.11$]. The MD of pain at rest at 24 h was also higher in trials at low risk of biases [5.05 (−0.07–0.69), $P=0.0003$] than in trials with unclear or high risks of biases [−0.31 (−2.84–2.22), $P=0.24$].

Visual inspection of funnel plots for morphine consumption highlighted asymmetry in the distribution of trials. The possibility of publication biases was supported by Egger test 2.6 (CI, 1.5–3.7). No such asymmetry was found in the funnel plot for pain [−0.81 (CI −1.9–0.3)] (Fig. 6).

Discussion

This is the first systematic review and meta-analysis of OIH in patients after surgery. It reveals that high intraoperative doses of remifentanil may slightly increase pain intensity at rest during the first postoperative 24 h, and moderately increase morphine use after surgery with no increase in morphine-related side-effects. The data we collected were insufficient data for similar analyses of other intraoperative opioids.

First quantitative review on OIH in surgical patients

Our review clearly confirms that high intraoperative doses of remifentanil results in hyperalgesia in patients after surgery; the available data are insufficient for conclusions to be drawn for fentanyl and sufentanil. Previous reviews on OIH were unable to obtain appropriate quantitative data on clinical consequences for patients.[25 26] We were able to identify 27 studies (60% of which were published after 2008) with a total of 1494 patients included. The data obtained were mostly for remifentanil-based anaesthesia allowing subgroup analysis on the type of intraoperative opioid. The heterogeneity of the data we collected was high ($I^2 > 50\%$) probably because of the diversity of the surgical models, protocols of intraoperative opioid administration, postoperative analgesia, and settings for measurements of pain on movement and hyperalgesia.

Our meta-analysis was based on numerous small trials conducted by academic researchers without sponsorship from the pharmaceutical industry. Our sensitivity analysis

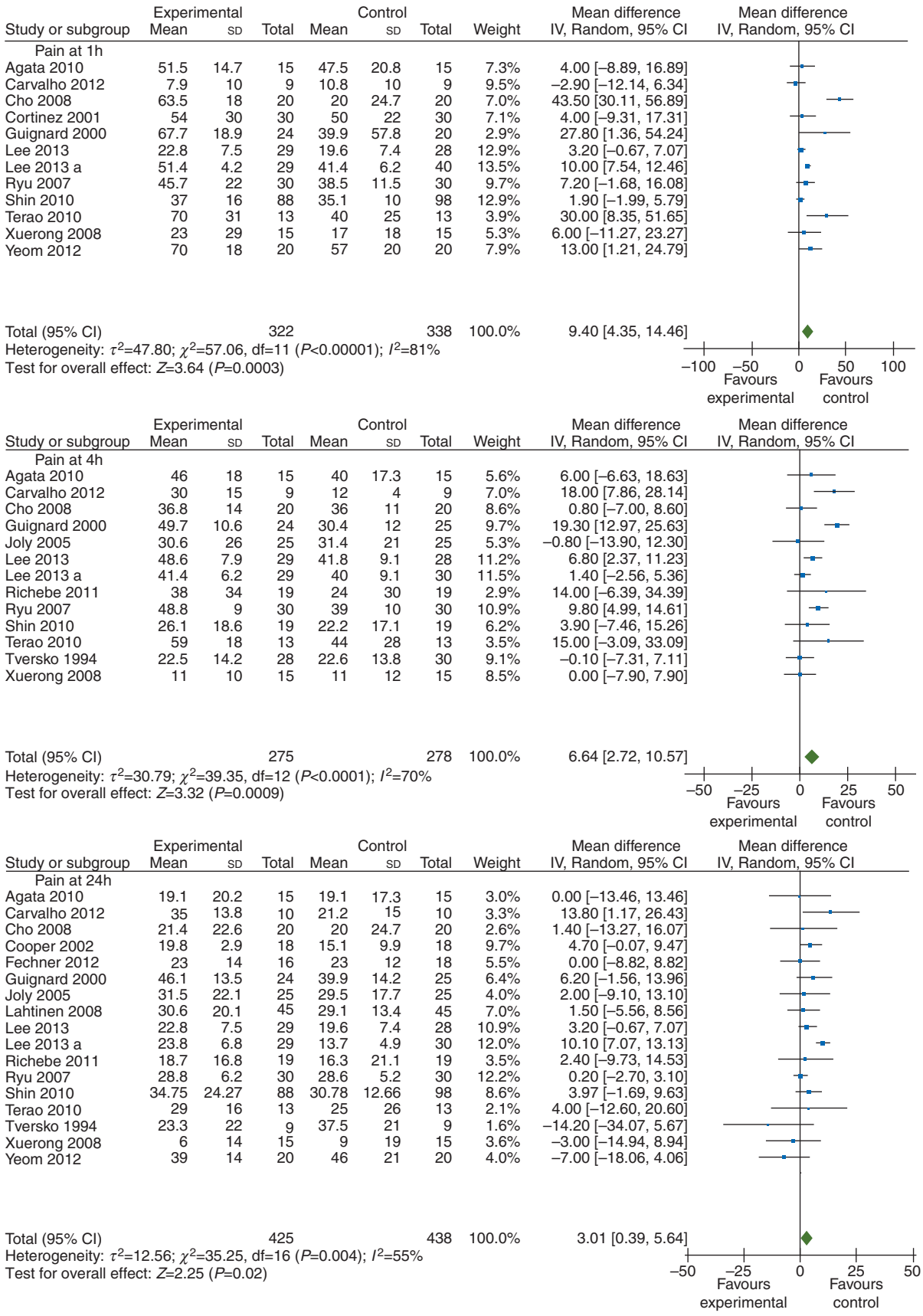

Fig 3 Forest plots of morphine titration and morphine consumption at 24 h. Pooled data analysis of the cumulative opioid consumption in adults receiving intraoperative opioid vs control. CI, confidence interval.

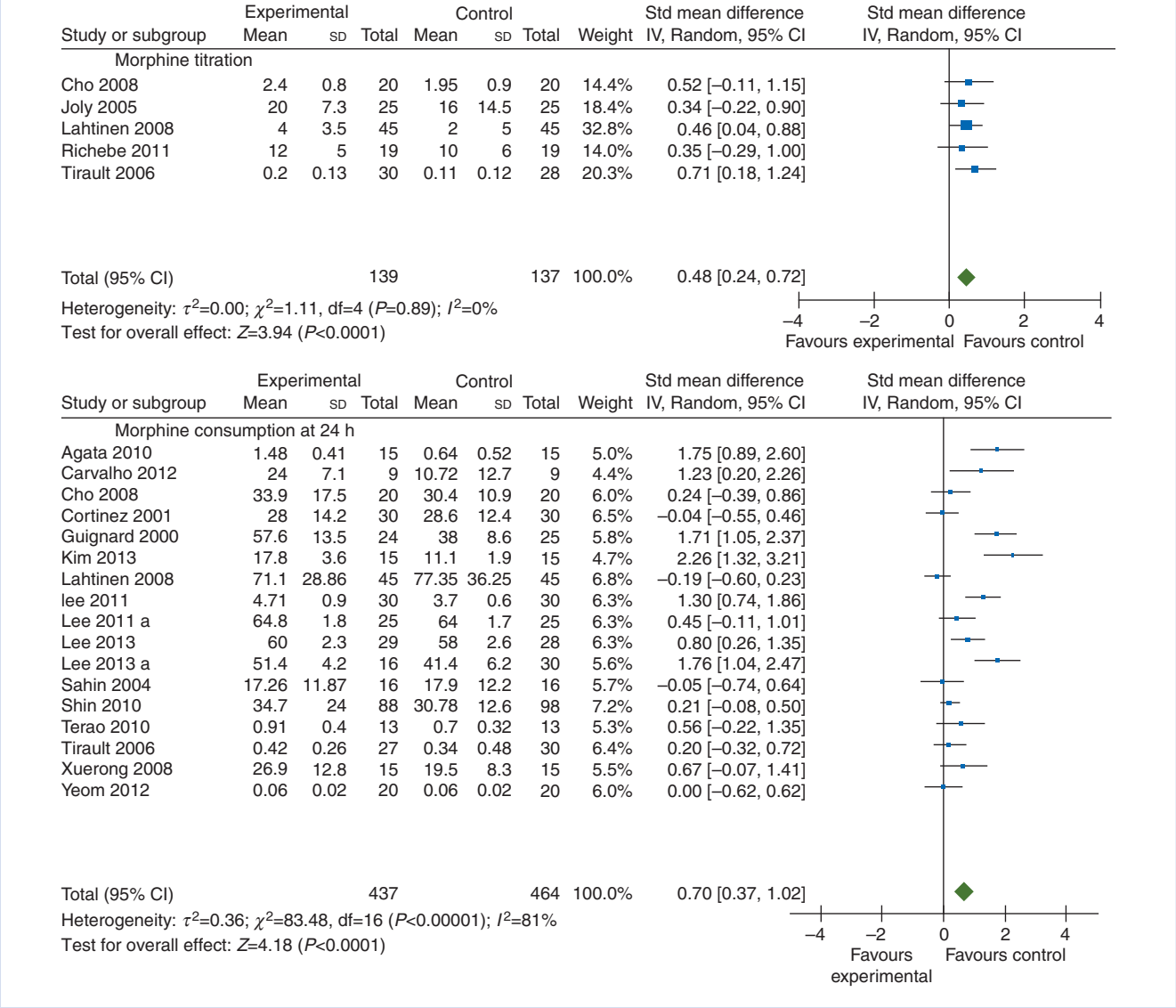

Fig 4 Forest plot of primary (A) and secondary hyperalgesia (B). Pooled data analysis of the primary hyperalgesia (pain threshold near the wound) or secondary hyperalgesia (area around the wound) in adults receiving intraoperative opioid vs control. CI, confidence interval.

clearly showed that trials with low risks of biases strengthened our results. However, our analysis also found that publication biases might lead to overestimation of OIH.

The clinical impact of remifentanil-induced hyperalgesia lasts for at least 24 h after surgery

A previous review concluded that there was not sufficient evidence to support or refute the existence of OIH in humans except in the case of normal volunteers.[26] However, we can now clearly demonstrate that high-dose intraoperative opioid causes a significant increase in postoperative pain intensity at rest persisting 24 h after surgery. The higher than control pain intensity at rest is greatest 1 h after surgery and then gradually decreases over 24 h. No such significant difference was found for pain on movement, but this may have been a consequence of the heterogeneity of the data and lack of statistical power. The immediate postoperative effect on pain intensity is certainly also associated with the unique pharmacokinetic profile of remifentanil with its rapid metabolism. Indeed, at all time points (i.e. 1, 4, and 24 h after surgery), the difference in pain intensity between treatment and control groups is because of data obtained for remifentanil-treated patients. Data on i.v. or intrathecal intraoperative fentanyl are less numerous, but our analyses suggest that high doses of fentanyl cause no significant modifications to the pain score at rest. The relative difference in pain intensity at rest peaked at 22% 1 h after surgery, when the mean pain at rest in the control groups was moderate (i.e. 39 on a VAS). According to a previous analysis of the clinical significance of differences in pain intensity, this peak would be considered to be a minimal aggravation of pain intensity.[55]

Consistent with these findings, we observed higher doses of morphine equivalent use 24 h after surgery among patients

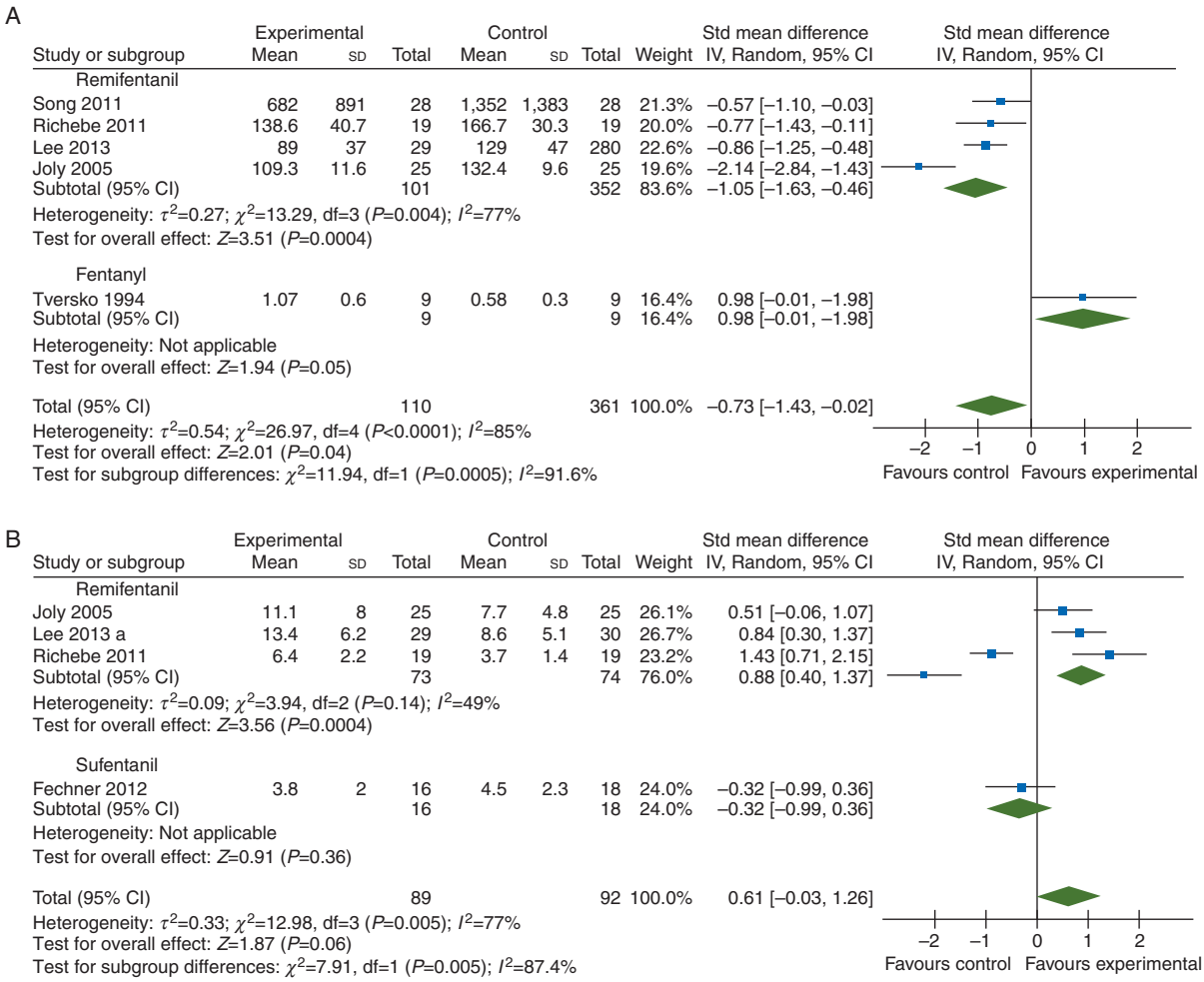

Fig 5 Funnel plot for pain at rest (A) and for morphine consumption at 24 h (B). Funnel plot to assess for publication bias.

Table 2 Side-effects for patients allocated to either experimental or control groups. CI, confidence interval

Comparison	Number of studies	Experimental	Control	Risk ratio (95% CI)	*P*-value	Heterogeneity (I^2) with random effect estimate (%)
Nausea	5	44/127	33/127	1.36 [0.97,1.9]	0.07	0
Vomiting	5	35/138	18/138	1.86 [0.69,5.01]	0.22	64
Nausea and vomiting	12	117/337	111/347	1.65 [0.84,1.31]	0.65	15
Drowsiness	5	47/120	48/119	0.96 [0.6,1.5]	0.87	51

exposed to high remifentanil doses; we estimated that an additional 18 mg of morphine equivalent were used over 24 h. This result reflects both the increased pain and potential acute tolerance phenomenon related to OIH. It is not possible in this type of clinical research setting to differentiate between hyperalgesia and tolerance as the mechanism for increased morphine use after surgery. The only clinical significance of the difference in postoperative morphine use is the related impact on the incidence of side-effects such as nausea, vomiting, and sedation.[56] A previous meta-regression analysis of the impact of non-steroidal anti-inflammatory agents on morphine-induced side-effects suggested that a 24-h morphine use difference of 10 mg may be associated with a 9% modification in the incidence of nausea and 3% of vomiting.[57] However, in our quantitative analysis, the estimated 18 mg mean increase in 24-h morphine use was not associated with a higher incidence of opioid-related side-effects after surgery. However, the value of this result is limited because only a small number of studies

Table 3 Subgroup analysis. MD, mean difference; SDM, standardized mean difference

Outcomes	Number of trials	Number of participants	Random effect (95% CI)	*P*-value	Heterogeneity (I^2) with random effect estimate (%)	Heterogeneity (I^2)—test for subgroup differences (%)
Morphine consumption (SMD)						
Type of opioid						0
Remifentanil	15	853	0.68 [0.32, 1.03]	0.0002	83	
Fentanyl i.v.	1	30	0.67 [−0.07, −1.41]	0.08	NA	
Fentanyl i.t.	1	18	1.23 [0.20, 2.26]	0.02	NA	
Type of anaesthesia						89.5
Propofol	6	341	0.01 [−0.21, 0.22]	0.96	0	
Inhalation anaesthetic agent	10	525	1.06 [0.56, 1.56]	0.0001	86	
Spinal anaesthesia	2	48	0.86 [0.26, 1.46]	0.005	0	
Type of comparison						0
High *vs* low doses	13	720	1.01 [0.54, 1.49]	<0.00001	87	
Opioid *vs* no opioid	6	228	0.63 [−0.09, 1.32]	0.09	82	
Pain at rest at 24 h (MD)						
Type of opioid						50.4
Remifentanil	14	759	3.26 [0.51, 6.1]	0.005	55	
Fentanyl i.v.	2	48	−5.97 [−16.21, 4.26]	0.34	0	
Fentanyl i.t.	2	56	7.29 [−0.76, 15.3]	0.19	43	
Type of anaesthesia						0
Propofol	6	290	3.40 [−0.49, 7.29]	0.09	11	
Inhalation anaesthetic agent	11	453	3.22 [−0.8, 7.2]	0.12	70	
Spinal anaesthesia	2	48	5.13 [−11.3, 21.5]	0.5	70	
Type of comparison						83.8
High *vs* low doses	11	456	5.78 [3.31, 8.25]	0.0001	13	
Opioid *vs* no opioid	9	367	0.72 [−2.42, 3.86]	0.65	20	

analysed the incidence of morphine-related side-effects associated, the methodology was heterogeneous and the number of patients included did not reach the optimal size of information and so was prone to Type II error.

Remifentanil-induced hyperalgesia can be measured in patients after surgery

Our results confirm that postoperative hyperalgesia can be detected in patients receiving high doses of intraoperative remifentanil. Six studies have measured the effects of intraoperative opioid administration on nociceptive thresholds.[11 20 41 42 50 52] Hyperalgesia was measured either as the pain threshold close to the surgical wound[11 20 41 42 50] or by evaluating secondary hyperalgesia extension around the wound.[11 20 21 52] These data were obtained mainly for remifentanil[11 20 41 52] although two studies addressed i.v. fentanyl and sufentanil.[21 42] It appears that remifentanil is responsible for measurable hyperalgesia, whereas fentanyl and sufentanil have no such effect. The wound pain threshold is reduced in patients receiving high-dose remifentanil. In animal research and experiments in volunteers to study OIH, remifentanil is the opioid that has been most extensively tested, but there are also data for fentanyl, morphine, and heroin,[3 4] suggesting a common hyperalgesic phenomenon for all opioids. However, our data suggest that in patients after surgery, only remifentanil induces measurable OIH.

The prevention of remifentanil-induced hyperalgesia in surgical patients

Factors including cumulative dose,[58] duration of administration,[58] and modality of withdrawal[59] have been discussed in the literature as possible determinant factors of remifentanil-induced hyperalgesia. Previous reviews have also suggested that dose may be an important factor.[25 26] Heterogeneous and insufficient data have precluded quantitative analysis of the pertinence of these factors on the development of remifentanil-induced hyperalgesia in patients after surgery. We were unable to define a cut-off value for remifentanil cumulative dose, infusion rate, or target effect site concentration, above which remifentanil might induce hyperalgesia. We only observed in the subgroup analysis of the type of comparison that a larger difference in remifentanil infusion was associated with a more significant effect on morphine use and pain intensity at rest. For the duration of remifentanil administration, the subgroup analysis with a cut-off value of 180 min of infusion did not reveal any significant differences. Owing to insufficient data, we were also unable to test whether the mode of withdrawal was a potential predictive factor for

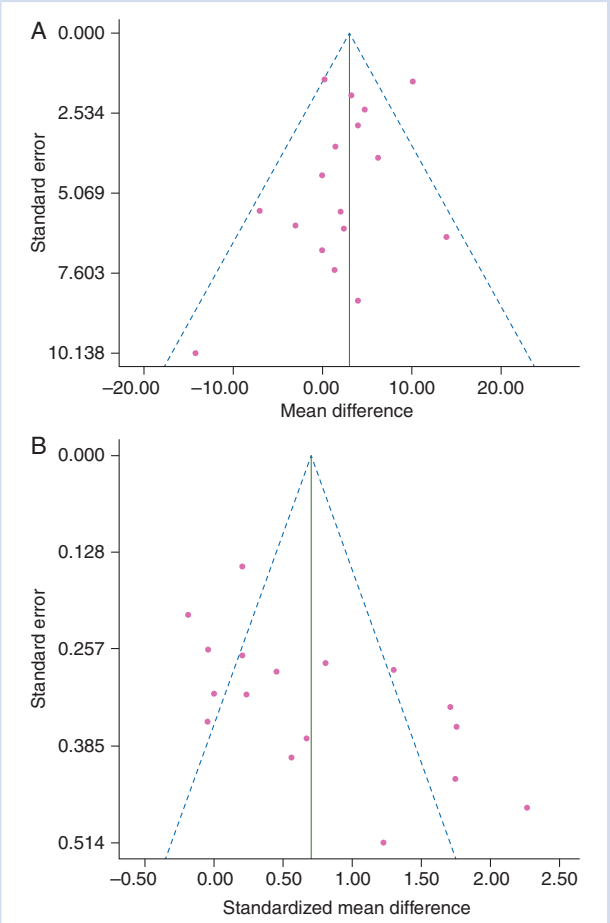

Fig 6 Funnel plot for pain at rest (A) and for morphine consumption at 24 h (B).

remifentanil-induced hyperalgesia. All of these factors are potential targets that may be exploited to minimize the pronociceptive effects of remifentanil without compromising the advantages of remifentanil analgesia.

Various pharmacological approaches have been tested to prevent remifentanil-induced hyperalgesia in patients after surgery, including perioperative ketamine,[11] magnesium,[60] propofol,[18] and nitrous oxide.[61] The data available were insufficient to test the impact of nitrous oxide on the development of remifentanil-induced hyperalgesia. However, our subgroup analysis suggests that propofol anaesthesia has a preventive effect on the development of remifentanil-induced hyperalgesia. In the studies using propofol-based anaesthesia, high-dose remifentanil was not associated with a difference in morphine consumption compared with studies using inhalation anaesthetic agents (sevoflurane, desflurane, or halothane) or regional anaesthesia. Similarly, there was no difference in pain at rest at 24 h, but this might be related to a limited sensitivity of pain intensity outcome measures because all patients were using patient-controlled analgesia. Furthermore, this result might be biased by the use of nitrous oxide in some of these studies. Reports of both experimental[62 63] and clinical research[64] suggest that nitrous oxide can prevent OIH. However, propofol has been shown to be able to prevent remifentanil-induced hyperalgesia in volunteers[65] and patients after surgery,[18] whereas sevoflurane has only weak anti-hyperalgesic effects in fentanyl-induced hyperalgesia in rat.[66] In conclusion, the prevention by propofol of the development of remifentanil-induced hyperalgesia and related consequences in patients after surgery deserve further clinical evaluation.

Implication for clinical practice and research

The clinical impact of remifentanil-induced hyperalgesia in the immediate postoperative period appears to be limited to a slight increase in pain intensity at rest persisting for 24 h after surgery, with a moderate increase in morphine use after surgery without any impact on the incidence of opioid-related side-effects. In view of these findings, we recommend that remifentanil should still be used during surgery. Although the evidence is not particularly robust, we suggest that remifentanil may be administered, preferentially, at the lowest possible dose and associated with propofol anaesthesia.

Future clinical trials should aim to clarify optimal remifentanil administration parameters that have an impact on the development of hyperalgesia (cumulative doses, site effect concentrations, and the protocols for withdrawal), and also investigate the possible preventive role of nitrous oxide and propofol during general anaesthesia, and the existence of spinal OIH. Experimental research has suggested long-lasting pronociceptive effects and anxiety-like behaviour related to OIH in rats[67 68] and preliminary clinical data suggest that OIH may contribute to the development of chronic post-surgical pain.[19] These possible long-lasting consequences of OIH deserve further clinical investigation in surgical patients.

Conclusion

Systematic review and meta-analysis of randomized, controlled studies revealed that the administration of high doses of remifentanil to patients during surgery is associated with a clinically small but statistically significant increase in their perception of pain.

Authors' contributions

D.F. participated in the conception of the review, acquisition, and interpretation of data, and drafting the article; V.M. participated in the conception of the review, acquisition, analysis, and interpretation of data, and drafting the article.

Acknowledgement

We thank Josefin Blomkvist for her help in the funnel plot construction.

Declaration of interest

None declared.

Funding

This work used only institutional resources.

References

1 Minville V, Fourcade O, Girolami JP, Tack I. Opioid-induced hyperalgesia in a mice model of orthopaedic pain: preventive effect of ketamine. *Br J Anaesth* 2010; **104**: 231–8

2 Vinik HR, Kissin I. Rapid development of tolerance to analgesia during remifentanil infusion in humans. *Anesth Analg* 1998; **86**: 1307–11

3 Larcher A, Laulin JP, Celerier E, Le Moal M, Simonnet G. Acute tolerance associated with a single opiate administration: involvement of N-methyl-D-aspartate-dependent pain facilitatory systems. *Neuroscience* 1998; **84**: 583–9

4 Celerier E, Laulin J, Larcher A, Le Moal M, Simonnet G. Evidence for opiate-activated NMDA processes masking opiate analgesia in rats. *Brain Res* 1999; **847**: 18–25

5 Katz J, Clairoux M, Redahan C, *et al.* High dose alfentanil pre-empts pain after abdominal hysterectomy. *Pain* 1996; **68**: 109–18

6 Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA. Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? *Br J Anaesth* 1997; **78**: 311–3

7 Chia YY, Liu K, Wang JJ, Kuo MC, Ho ST. Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. *Can J Anaesth* 1999; **46**: 872–7

8 Schraag S, Checketts MR, Kenny GN. Lack of rapid development of opioid tolerance during alfentanil and remifentanil infusions for postoperative pain. *Anesth Analg* 1999; **89**: 753–7

9 Guignard B, Bossard AE, Coste C, *et al.* Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. *Anesthesiology* 2000; **93**: 409–17

10 Cortinez LI, Brandes V, Munoz HR, Guerrero ME, Mur M. No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. *Br J Anaesth* 2001; **87**: 866–9

11 Joly V, Richebe P, Guignard B, *et al.* Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. *Anesthesiology* 2005; **103**: 147–55

12 Lee JR, Jung CW, Lee YH. Reduction of pain during induction with target-controlled propofol and remifentanil. *Br J Anaesth* 2007; **99**: 876–80

13 Crawford MW, Hickey C, Zaarour C, Howard A, Naser B. Development of acute opioid tolerance during infusion of remifentanil for pediatric scoliosis surgery. *Anesth Analg* 2006; **102**: 1662–7

14 Schmidt S, Bethge C, Forster MH, Schafer M. Enhanced postoperative sensitivity to painful pressure stimulation after intraoperative high dose remifentanil in patients without significant surgical site pain. *Clin J Pain* 2007; **23**: 605–11

15 Lahtinen P, Kokki H, Hynynen M. Remifentanil infusion does not induce opioid tolerance after cardiac surgery. *J Cardiothorac Vasc Anesth* 2008; **22**: 225–9

16 Aubrun F, Valade N, Coriat P, Riou B. Predictive factors of severe postoperative pain in the postanesthesia care unit. *Anesth Analg* 2008; **106**: 1535–41

17 Xuerong Y, Yuguang H, Xia J, Hailan W. Ketamine and lornoxicam for preventing a fentanyl-induced increase in postoperative morphine requirement. *Anesth Analg* 2008; **107**: 2032–7

18 Shin SW, Cho AR, Lee HJ, *et al.* Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. *Br J Anaesth* 2010; **105**: 661–7

19 Salengros JC, Huybrechts I, Ducart A, *et al.* Different anesthetic techniques associated with different incidences of chronic postthoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. *J Cardiothorac Vasc Anesth* 2010; **24**: 608–16

20 Richebe P, Pouquet O, Jelacic S, *et al.* Target-controlled dosing of remifentanil during cardiac surgery reduces postoperative hyperalgesia. *J Cardiothorac Vasc Anesth* 2011; **25**: 917–25

21 Fechner J, Ihmsen H, Schuttler J, Jeleazcov C. The impact of intra-operative sufentanil dosing on post-operative pain, hyperalgesia and morphine consumption after cardiac surgery. *Eur J Pain* 2013; **17**: 562–70

22 Seymour RA, Rawlins MD, Rowell FJ. The Lancet – Saturday 26 June 1982. *Lancet* 1982; **1**: 1425–6

23 Marshall H, Porteous C, McMillan I, MacPherson SG, Nimmo WS. Relief of pain by infusion of morphine after operation: does tolerance develop? *Br Med J (Clin Res Ed)* 1985; **291**: 19–21

24 Hill HF, Chapman CR, Kornell JA, Sullivan KM, Saeger LC, Benedetti C. Self-administration of morphine in bone marrow transplant patients reduces drug requirement. *Pain* 1990; **40**: 121–9

25 Angst MS, Clark JD. Opioid-induced hyperalgesia: a qualitative systematic review. *Anesthesiology* 2006; **104**: 570–87

26 Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS. Do opioids induce hyperalgesia in humans? An evidence-based structured review. *Pain Med* 2009; **10**: 829–39

27 Martinez V, Fletcher D. Prevention of opioid-induced hyperalgesia in surgical patients: does it really matter? *Br J Anaesth* 2012; **109**: 302–4

28 Higgins JPT, Green S. Chapter 4: Guide to the contents of a Cochrane protocol and review. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.1*. The Cochrane Collaboration. Available from www.cochrane-handbook.org (2008) (accessed 18 April 2014)

29 Liberati A, Altman DG, Tetzlaff J, *et al.* The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700

30 Lefebvre C, Manheimer E, Glanville J. Chapter 6.4: Searching for studies. In: Higgins JPT, Green S, eds. *Cochrane Handbook for Systematic Reviews of Interventions, Version 5.0.1*. The Cochrane Collaboration. Available from www.cochrane-handbook.org (2008) (accessed 18 April 2014)

31 Higgins JP, White IR, Wood AM. Imputation methods for missing outcome data in meta-analysis of clinical trials. *Clin Trials* 2008; **5**: 225–39

32 Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13

33 Kay B. A clinical investigation of piritramide in the treatment of postoperative pain. *Br J Anaesth* 1971; **43**: 1167–71

34 Schug S, Gandham N. Opioids: clinical use. In: MacMahon SB, Koltzenburg M, eds. *Wall and Melzack's Textbook of Pain*, 5th edn. Philadelphia: Elsevier Churchill Livingstone, 2006; 443–57

35 Stoelting R, Hilier S. Opioid agonists and antagonists, pharmacology and physiology. In: Wilkins LW, ed. *Anesthetic Practice*, 4th edn. Philadelphia: Elsevier Churchill Livingstone, 2006; 87–126

36 Cohen J. *Statistical Power Analysis for the Behavioral Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates, 1988

37 Gerbershagen HJ, Aduckathil S, van Wijck AJ, Peelen LM, Kalkman CJ, Meissner W. Pain intensity on the first day after surgery: a prospective cohort study comparing 179 surgical procedures. *Anesthesiology* 2013; **118**: 934–44

38 Terao Y. Intraoperative magnesium sulphate does not suppress remifentanyl-induced acute opioids tolerance and hyperalgesia in surgical patients. *Eur Soc Anesthesiol* 2010; **27**: 208

39 Tirault M, Derrode N, Clevenot D, Rolland D, Fletcher D, Debaene B. The effect of nefopam on morphine overconsumption induced by large-dose remifentanil during propofol anesthesia for major ab-

dominal surgery. *Anesth Analg* 2006; **102**: 110–7

40 Cho AR, Kim HH, Kim KH, Jung KY, Kim WS, Kwon JY. Effect of remifentanil on postoperative pain in gynecologic surgery with sevoflurane anesthesia. *Korean J Anesthesiol* 2008; **55**: 182–8

41 Lee C, Kim YD, Kim JN. Antihyperalgesic effects of dexmedetomidine on high-dose remifentanil-induced hyperalgesia. *Korean J Anesthesiol* 2013; **64**: 301–7

42 Tverskoy M, Oz Y, Isakson A, Finger J, Bradley EL Jr, Kissin I. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. *Anesth Analg* 1994; **78**: 205–9

43 Hansen EG, Duedahl TH, Romsing J, Hilsted KL, Dahl JB. Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. *Acta Anaesthesiol Scand* 2005; **49**: 1464–70

44 Carvalho B, Drover DR, Ginosar Y, Cohen SE, Riley ET. Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance. *Int J Obstet Anesth* 2012; **21**: 29–34

45 Cooper DW, Garcia E, Mowbray P, Millar MA. Patient-controlled epidural fentanyl following spinal fentanyl at Caesarean section. *Anaesthesia,* 2002; **57**: 266–70

46 Sahin A, Canbay O, Cuhadar A, Celebi N, Aypar U. Bolus ketamine does not decrease hyperalgesia after remifentanil infusion. *Pain Clinic* 2004; **16**: 407–11

47 Yeom JH, Kim KH, Chon MS, Byun J, Cho SY. Remifentanil used as adjuvant in general anesthesia for spinal fusion does not exhibit acute opioid tolerance. *Korean J Anesth* 2012; **63**: 103–7

48 Lee C, Song YK, Jeong HM, Park SN. The effects of magnesium sulfate infiltration on perioperative opioid consumption and opioid-induced hyperalgesia in patients undergoing robot-assisted laparoscopic prostatectomy with remifentanil-based anesthesia. *Korean J Anesth* 2011; **61**: 244–50

49 Lee C, Song YK, Lee JH, Ha SM. The effects of intraoperative adenosine infusion on acute opioid tolerance and opioid induced hyperalgesia induced by remifentanil in adult patients undergoing tonsillectomy. *Korean J Pain,* 2011; **24**: 7–12

50 Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg* 2011; **113**: 390–7

51 Kim S-H, Lee MH, Seo H, Lee I-G, Hong J-Y, Hwang J-H. Intraoperative infusion of 0.6–0.9 $\mu g\,kg^{-1}\,min^{-1}$ remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. *Anesthesiology,* 2013; **118**: 337–43

52 Lee C, Lee HW, Kim JN. Effect of oral pregabalin on opioid-induced hyperalgesia in patients undergoing laparo-endoscopic single-site urologic surgery. *Korean J Anesthesiol* 2013; **64**: 19–24

53 Agata H, Yumura J, Miki M, Koitabashi T. High dose remifentanil administration during orthognathic surgery is associated with postoperative hyperalgesia. *J Jpn Dental Soc Anesthesiol* 2010; **38**: 13–20

54 Ryu SH, Lee DW, Kwon JY. The effect of remifentanil with sevoflurane in subtotal gastrectomy patients with patient controlled epidural analgesia. *Korean J Anesthesiol* 2007; **53**: 35–41

55 Cepeda MS, Africano JM, Polo R, Alcala R, Carr DB. What decline in pain intensity is meaningful to patients with acute pain? *Pain* 2003; **105**: 151–7

56 Kehlet H. Postoperative pain relief—what is the issue? *Br J Anaesth* 1994; **72**: 375–8

57 Marret E, Flahault A, Samama CM, Bonnet F. Effects of postoperative, nonsteroidal, antiinflammatory drugs on bleeding risk after tonsillectomy: meta-analysis of randomized, controlled trials. *Anesthesiology* 2003; **98**: 1497–502

58 Cabanero D, Puig MM. Immediate and delayed remifentanil-induced hypersensitivity. *Anesth Analg* 2012; **115**: 977–8; author reply 8–9

59 Drdla R, Gassner M, Gingl E, Sandkuhler J. Induction of synaptic long-term potentiation after opioid withdrawal. *Science* 2009; **325**: 207–10

60 Song JW, Lee YW, Yoon KB, Park SJ, Shim YH. Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. *Anesth Analg* 2011; **113**: 390–7

61 Echevarria G, Elgueta F, Fierro C, *et al.* Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil-propofol anaesthesia in humans. *Br J Anaesth* 2011; **107**: 959–65

62 Richebe P, Rivat C, Creton C, *et al.* Nitrous oxide revisited: evidence for potent antihyperalgesic properties. *Anesthesiology* 2005; **103**: 845–54

63 Bessiere B, Richebe P, Laboureyras E, Laulin JP, Contarino A, Simonnet G. Nitrous oxide (N_2O) prevents latent pain sensitization and long-term anxiety-like behavior in pain and opioid-experienced rats. *Neuropharmacology* 2007; **53**: 733–40

64 Echevarria G, Elgueta F, Fierro C, *et al.* Nitrous oxide (N(2)O) reduces postoperative opioid-induced hyperalgesia after remifentanil–propofol anaesthesia in humans. *Br J Anaesth* 2011; **107**: 959–65

65 Singler B, Troster A, Manering N, Schuttler J, Koppert W. Modulation of remifentanil-induced postinfusion hyperalgesia by propofol. *Anesth Analg* 2007; **104**: 1397–403

66 Richebe P, Rivalan B, Rivat C, *et al.* Effects of sevoflurane on carrageenan- and fentanyl-induced pain hypersensitivity in Sprague-Dawley rats. *Can J Anaesth* 2009; **56**: 126–35

67 Bessiere B, Laboureyras E, Ben Boujema M, Laulin JP, Simonnet G. A high-dose of fentanyl induced delayed anxiety-like behavior in rats. Prevention by a NMDA receptor antagonist and nitrous oxide (N(2)O). *Pharmacol Biochem Behav* 2012; **102**: 562–8

68 Rivat C, Laulin JP, Corcuff JB, Celerier E, Pain L, Simonnet G. Fentanyl enhancement of carrageenan-induced long-lasting hyperalgesia in rats: prevention by the N-methyl-D-aspartate receptor antagonist ketamine. *Anesthesiology* 2002; **96**: 381–91

Handling editor: L. Colvin