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

D. Fletcher1,2,3* and V. Martinez1,2,3

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
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. 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. If medians with range were reported, medians and sds were obtained with the formulae reported by Hozo and colleagues. 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, 1.33 for i.v. oxycodone, 5 for i.v. hydromorphone and 100 for fentanyl). 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, mg kg -1 24 h 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. 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 x median sd. The sd was calculated from the sd of each surgical model in all included studies according to a
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 1674 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. Following our requests for additional information to obtain missing values, three authors provided additional data. The estimation of the median SD was 27 mg.

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, all three of which were at low risk of bias for selective reporting.

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 and for sufentanil trials (Fig. 5). In the remifentanil subgroup, SMD for both primary hyperalgesia and secondary hyperalgesia were substantially different (Fig. 5).
Electronic search: 703 references identified
187 PUBMED/304 EMBASE/192 COCHRANE library/20 LILACS

- 107 deduplication
- 596 as candidates for selection
- 487 eliminated by selection on title
- 109 selected on title after consensus
- 72 eliminated by selection on abstract
- 37 selected on abstract after consensus
- 11 eliminated by selection on full text
  - 2 duplications
  - 6 due to study design
  - 2 due to different analgesia for the different groups
  - 1 unusable conference proceeding
- 26 references selected on full text
- 1 unpublished abstract identified
- 0 identified as terminated and unpublished

27 articles included in the systematic review
Remifentanil=21, Fentanyl i.v.=2, Sufentanil i.v.=1, Fentanyl i.t.=3
Data from 25 articles included in the meta-analysis

Hand searching of ASA and ESA congresses from 2008 to 2013

Clinical trial.gov registers: 42 references identified
- 36 with inappropriate study design
- 3 terminated and identified in the electronic search
- 3 ongoing

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.

<table>
<thead>
<tr>
<th>Study (first author, year)</th>
<th>Number of patients in control or low opioid dose group</th>
<th>Number of patients in high opioid dose group</th>
<th>Patients/surgery</th>
<th>Intervention</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agata⁴ᴬ (2010)</td>
<td>15 low dose</td>
<td>15</td>
<td>Elective</td>
<td>I.V. remifentanil (0.15 μg kg⁻¹ min⁻¹) vs (≥ 0.3 μg kg⁻¹ min⁻¹)</td>
<td>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</td>
</tr>
<tr>
<td>Carvalho⁴⁴ (2012)</td>
<td>9 control</td>
<td>9 low dose</td>
<td>Caesarean section</td>
<td>Intrathecal single shot fentanyl (5 μg) vs (25 μg)</td>
<td>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</td>
</tr>
<tr>
<td>Chia⁷ (1999)</td>
<td>30 low dose</td>
<td>30</td>
<td>Hysterectomy</td>
<td>1 μg kg⁻¹ fentanyl bolus vs 15 μg kg⁻¹ bolus plus 100 μg h⁻¹ infusion</td>
<td>Pain VAS at rest 4, 8, 12, and 16 h. Haemodynamic, arterial blood gas, and sedation scores. PCA i.v. morphine 24 h</td>
</tr>
<tr>
<td>Cho⁴⁰ (2008)</td>
<td>30 control</td>
<td>30 low dose</td>
<td>Gynaecology</td>
<td>I.V. remifentanil (target 1 ng ml⁻¹) vs high-dose remifentanil (target 3 ng ml⁻¹)</td>
<td>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 treatment</td>
</tr>
<tr>
<td>Cooper⁶ (1997)</td>
<td>30 control</td>
<td>30</td>
<td>Caesarean section</td>
<td>Intrathecal single shot fentanyl (25 μg) vs placebo</td>
<td>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</td>
</tr>
<tr>
<td>Cooper⁴⁶ (2002)</td>
<td>18 control</td>
<td>18</td>
<td>Caesarean section</td>
<td>Intrathecal single shot fentanyl (25 μg) vs placebo</td>
<td>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 analgesia</td>
</tr>
<tr>
<td>Cortinez⁴⁰ (2001)</td>
<td>30 control</td>
<td>30</td>
<td>Gynaecology</td>
<td>I.V. remifentanil (0.23 μg kg⁻¹ min⁻¹) vs placebo</td>
<td>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</td>
</tr>
<tr>
<td>Fechner⁴¹ (2013)</td>
<td>18 low dose</td>
<td>16</td>
<td>Coronary artery bypass graft</td>
<td>I.V. sufentanil (target 0.4 ng ml⁻¹) vs remifentanil (target 0.8 ng ml⁻¹)</td>
<td>Pain NRS at rest and during deep inspiration, PCA i.v. morphine 48 h. Cognitive function, sedation, constipation, PONV. Primary and secondary hyperalgesia</td>
</tr>
<tr>
<td>Guignard⁴⁸ (2000)</td>
<td>25 low dose</td>
<td>24</td>
<td>Colorectal surgery</td>
<td>I.V. remifentanil (0.1 μg kg⁻¹ min⁻¹) vs (0.3 μg kg⁻¹ min⁻¹)</td>
<td>Pain VAS at rest 24 h. PCA i.v. morphine 48 h. PON, PO, pruritus, dysphoria, diplopia, hallucinations</td>
</tr>
<tr>
<td>Hansen⁶³ (2005)</td>
<td>18 control</td>
<td>21</td>
<td>Major abdominal surgery</td>
<td>I.V. remifentanil (0.4 μg kg⁻¹ min⁻¹) vs placebo</td>
<td>Summed pain VAS at rest and during coughing at 4, 6, and 24 h. PCA i.v. morphine 24 h, PON, PO, sedation</td>
</tr>
<tr>
<td>Joly¹¹ (2005)</td>
<td>25 low dose</td>
<td>25</td>
<td>Major abdominal surgery</td>
<td>I.V. remifentanil (0.05 μg kg⁻¹ min⁻¹) vs (0.4 μg kg⁻¹ min⁻¹)</td>
<td>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</td>
</tr>
<tr>
<td>Kim⁵¹ (2013)</td>
<td>15 control</td>
<td>15</td>
<td>Paediatric urology</td>
<td>I.V. remifentanil (0.3 μg kg⁻¹ min⁻¹) vs (0.3 μg kg⁻¹ min⁻¹)</td>
<td>Pain CHEOPS scale at rest. Parent-node controlled i.v. fentanyl analgesia. PO, drowsiness, pruritus</td>
</tr>
<tr>
<td>Lahtinen⁴⁵ (2008)</td>
<td>45 control</td>
<td>45</td>
<td>Cardiac surgery</td>
<td>I.V. remifentanil (0.3 μg kg⁻¹ min⁻¹) vs placebo</td>
<td>Pain VAS at rest and during deep breath every 8 h during 48 h. PCA i.v. oxycodone 48 h. PON, PO, sedation</td>
</tr>
</tbody>
</table>

Continued...
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
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 \(0.32 (0.22) \mu\text{g kg}^{-1}\text{min}^{-1}\) than in trials comparing remifentanil and placebo \(0.18 (0.12) \mu\text{g kg}^{-1}\text{min}^{-1}\). 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.
Opioid-induced hyperalgesia in patients 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. 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 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).

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

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. 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 a minimal aggravation of pain intensity. 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).

Consistent with these findings, we observed higher doses of morphine equivalent use 24 h after surgery among patients...
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. 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. 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>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Experimental Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Std mean difference IV, Random, 95% CI</th>
<th>Std mean difference IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Song 2011</td>
<td>682</td>
<td>891</td>
<td>28</td>
<td>1,352</td>
<td>1,383</td>
<td>28</td>
<td>21.3%</td>
<td>–0.57 [–1.10, –0.03]</td>
<td></td>
</tr>
<tr>
<td>Richebe 2011</td>
<td>138.6</td>
<td>40.7</td>
<td>19</td>
<td>166.7</td>
<td>30.3</td>
<td>19</td>
<td>20.0%</td>
<td>–0.77 [–1.43, –0.11]</td>
<td></td>
</tr>
<tr>
<td>Lee 2005</td>
<td>89</td>
<td>37</td>
<td>29</td>
<td>129</td>
<td>47</td>
<td>280</td>
<td>22.6%</td>
<td>–0.86 [–1.25, –0.48]</td>
<td></td>
</tr>
<tr>
<td>Joly 2005</td>
<td>109.3</td>
<td>11.6</td>
<td>25</td>
<td>132.4</td>
<td>9.6</td>
<td>25</td>
<td>19.6%</td>
<td>–2.14 [–2.84, –1.43]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: r²=0.27; X²=13.29, df=3 (P=0.004); I²=77%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=3.51 (P=0.0004)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenetyl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tversko 1994</td>
<td>1.07</td>
<td>0.6</td>
<td>9</td>
<td>0.58</td>
<td>0.3</td>
<td>9</td>
<td>16.4%</td>
<td>0.98 [0.91, 1.98]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>–0.73 [–1.43, –0.02]</td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: r²=0.54; X²=26.97, df=4 (P=0.0001); I²=85%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=2.01 (P=0.04)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: X²=11.94, df=1 (P=0.0005); I²=91.6%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Number of studies</th>
<th>Experimental</th>
<th>Control</th>
<th>Risk ratio (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity (I²) with random effect estimate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>5</td>
<td>44/127</td>
<td>33/127</td>
<td>1.36 [0.97,1.9]</td>
<td>0.07</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>5</td>
<td>35/138</td>
<td>18/138</td>
<td>1.86 [0.69,5.01]</td>
<td>0.22</td>
<td>64</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>12</td>
<td>117/337</td>
<td>111/347</td>
<td>1.65 [0.84,1.31]</td>
<td>0.65</td>
<td>15</td>
</tr>
<tr>
<td>Drowsiness</td>
<td>5</td>
<td>47/120</td>
<td>48/119</td>
<td>0.96 [0.69,1.5]</td>
<td>0.87</td>
<td>51</td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/bja/article-abstract/112/6/991/243753 by guest on 29 July 2018
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

Hyperalgesia was measured either as the pain threshold close to the surgical wound11 20 41 42 50 52 or by evaluating secondary hyperalgesia extension around the wound.11 20 21 52 These data were obtained mainly for remifentanil11 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 withdrawal59 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 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

<p>| Table 3 Subgroup analysis. MD, mean difference; SDM, standardized mean difference |
|------------------|------------------|------------------|------------------|------------------|</p>
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Number of trials</th>
<th>Number of participants</th>
<th>Random effect (95% CI)</th>
<th>P-value</th>
<th>Heterogeneity (I²) with random effect estimate (%)</th>
<th>Heterogeneity (I²)—test for subgroup differences (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine consumption (SMD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>15</td>
<td>853</td>
<td>0.68 [0.32, 1.03]</td>
<td>0.0002</td>
<td>83</td>
<td>0</td>
</tr>
<tr>
<td>Fentanyl i.v.</td>
<td>1</td>
<td>30</td>
<td>0.67 [−0.07, −1.41]</td>
<td>0.08</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fentanyl i.t.</td>
<td>1</td>
<td>18</td>
<td>1.23 [0.20, 2.26]</td>
<td>0.02</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Type of anaesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>6</td>
<td>341</td>
<td>0.01 [−0.21, 0.22]</td>
<td>0.96</td>
<td>0</td>
<td>89.5</td>
</tr>
<tr>
<td>Inhalation anaesthetic agent</td>
<td>10</td>
<td>525</td>
<td>1.06 [0.56, 1.56]</td>
<td>0.0001</td>
<td>86</td>
<td>0</td>
</tr>
<tr>
<td>Spinal anaesthesia</td>
<td>2</td>
<td>48</td>
<td>0.86 [0.26, 1.46]</td>
<td>0.005</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>Type of comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High vs low doses</td>
<td>13</td>
<td>720</td>
<td>1.01 [0.54, 1.49]</td>
<td>&lt;0.00001</td>
<td>87</td>
<td>0</td>
</tr>
<tr>
<td>Opioid vs no opioid</td>
<td>6</td>
<td>228</td>
<td>0.63 [−0.09, 1.32]</td>
<td>0.09</td>
<td>82</td>
<td>82</td>
</tr>
<tr>
<td>Pain at rest at 24 h (MD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of opioid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Remifentanil</td>
<td>14</td>
<td>759</td>
<td>3.26 [0.51, 6.1]</td>
<td>0.005</td>
<td>55</td>
<td>5</td>
</tr>
<tr>
<td>Fentanyl i.v.</td>
<td>2</td>
<td>48</td>
<td>−5.97 [−16.21, 4.26]</td>
<td>0.34</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Fentanyl i.t.</td>
<td>2</td>
<td>56</td>
<td>7.29 [−0.76, 15.3]</td>
<td>0.19</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>Type of anaesthesia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Propofol</td>
<td>6</td>
<td>290</td>
<td>3.40 [−0.49, 7.29]</td>
<td>0.09</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Inhalation anaesthetic agent</td>
<td>11</td>
<td>453</td>
<td>3.22 [−0.8, 7.2]</td>
<td>0.12</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Spinal anaesthesia</td>
<td>2</td>
<td>48</td>
<td>5.13 [−11.3, 21.5]</td>
<td>0.5</td>
<td>70</td>
<td>70</td>
</tr>
<tr>
<td>Type of comparison</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High vs low doses</td>
<td>11</td>
<td>456</td>
<td>5.78 [3.31, 8.25]</td>
<td>0.0001</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Opioid vs no opioid</td>
<td>9</td>
<td>367</td>
<td>0.72 [−2.42, 3.86]</td>
<td>0.65</td>
<td>20</td>
<td>20</td>
</tr>
</tbody>
</table>

Downloaded from https://academic.oup.com/bja/article-abstract/112/6/991/243753 by guest on 29 July 2018
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 experimental62 63 and clinical research64 suggest that nitrous oxide can prevent OIH. However, propofol has been shown to be able to prevent remifentanil-induced hyperalgesia in volunteers65 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 rats67 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

31. Tirault M, Derrode N, Clevenot D, Fletcher D, Debœne B. The effect of nefopam on morphine overconsumption induced by large-dose remifentanil during propofol anesthesia for major ab-
45 Cooper DW, Garcia E, Mowbray P, Millar MA. Patient-controlled epidural fentanyl following spinal fentanyl at Caesarean section. Anaesthesia, 2002; 57: 266–70
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
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
58 Cobanero D, Puig MM. Immediate and delayed remifentanil-induced hypersensitivity. Anesth Analg 2012; 115: 977–8; author reply 8–9

Handling editor: L. Colvin