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UNIVERSITE DE LAUSANNE - FACULTE DE BIOLOGIE ET DE MEDECINE
Département des services de chirurgie et d'anesthésiologie
Service d'anesthésiologie

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préparée sous la direction du Docteur Eric ALBRECHT

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

Jonathan FRAUENKNECHT

Médecin diplômé de la Confédération Suisse
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Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis

Lausanne, le 6 février 2020

pour Le Doyen
de la Faculté de Biologie et de Médecine

Monsieur le Professeur John Prior
Vice-Directeur de l'Ecole doctorale

Efficacité analgésique d'une anesthésie avec opioïdes versus sans opioïdes : une revue systématique de la littérature avec méta-analyses

[Analgesic impact of intra-operative opioids versus opioid free anesthesia: a systematic review and meta-analysis]

Les opioïdes sont administrés durant l'intervention afin de contrôler la réponse sympathique à un stimulus chirurgical, mais aussi pour soulager la douleur postopératoire. Récemment, l'utilisation des opioïdes durant la chirurgie a été remise en question en raison de l'absence probable de bénéfice dans la phase postopératoire immédiat, mais aussi en raison des effets secondaires, tels que les nausées et vomissements postopératoires.

Le but de cette méta-analyse est d'investiguer si l'utilisation d'opioïde intraopératoire comparée à une stratégie sans opioïde permet de diminuer les douleurs postopératoires sans augmenter le taux de nausées et vomissements postopératoires.

Nous avons inclus des essais cliniques randomisés et contrôlés effectués chez des patients adultes pour tout type de chirurgie qui ont étudié l'efficacité analgésique postopératoire d'une administration intraopératoire d'opioïde avec soit l'administration d'un placebo, soit l'absence d'administration.

L'analyse des 23 études identifiées avec plus de 1300 patients inclus a démontré que les scores de douleurs au repos (échelle de 0 à 10, 0 étant aucune douleur et 10 la pire douleur imaginable) à 2h postopératoire étaient équivalents dans les deux groupes, avec une différence moyenne (IC 95%) de 0,2 point (-0,2 à 0,5), p=0,38. Les taux de nausées et vomissements postopératoires étaient de 24% dans le groupe avec opioïde et 19% dans le groupe sans ce qui représente un risque relatif (IC 95%) de 0,77 (0,61 à 0,97), p=0,03.

En conclusion, l'utilisation d'opioïde intraopératoire ne diminue pas les douleurs postopératoires, mais est associée à une augmentation des nausées et vomissements postopératoire.

Anaesthesia 2019, 74, 651–662 doi:10.1111/anae.14582

Review Article

Analgesic impact of intra-operative opioids vs. opioid-free anaesthesia: a systematic review and meta-analysis

J. Frauenknecht,[1] **K. R. Kirkham,**[2] **A. Jacot-Guillarmod**[3] and **E. Albrecht**[4]

1 Resident, 3 Research Assistant, 4 Program Director of Regional Anaesthesia, Department of Anaesthesia, Lausanne University Hospital, Lausanne, Switzerland
2 Consultant, Department of Anaesthesia, Toronto Western Hospital, University of Toronto, Toronto, Canada

Summary

Opioids are administered peri-operatively for postoperative analgesia, and intra-operatively to control the sympathetic response to surgical stimuli, frequently as a surrogate for presumed pain. However, opioid use during surgery is a matter of dispute in contemporary practice and carries the risk of side-effects such as postoperative nausea and vomiting. This meta-analysis investigated whether opioid-inclusive, compared with opioid-free anaesthesia, would reduce postoperative pain, without increasing the rate of postoperative nausea and vomiting. The electronic databases Medline and PubMed were searched until June 2018. We included trials investigating pain outcomes and comparing any type of intra-operative opioid administration with placebo injection or no intra-operative opioid. Most meta-analyses were performed using a random effects model. We rated the quality of evidence for each outcome. The primary outcome was pain score at rest (analogue scale, 0–10) at two postoperative hours. Our secondary outcomes included the rate of postoperative nausea and vomiting within the first 24 postoperative hours and length of stay in the recovery area. Twenty-three randomised controlled trials, including 1304 patients, were identified. Pain scores at rest at two postoperative hours were equivalent in the opioid-inclusive and opioid-free groups with a mean difference (95%CI) of 0.2 (−0.2 to 0.5), I^2 = 83%, p = 0.38 and a high quality of evidence. Similarly, there was high-quality evidence that the rate of postoperative nausea and vomiting was reduced in the opioid-free group, with a risk ratio (95%CI) of 0.77 (0.61–0.97), I^2 = 16%, p = 0.03 and high-quality evidence for a similar length of stay in the recovery area, the mean difference (95%CI) being 0.6 (−8.2 to 9.3), min, I^2 = 60%, p = 0.90. As there is strong evidence that opioid-inclusive anaesthesia does not reduce postoperative pain, but is associated with more postoperative nausea and vomiting, when compared with opioid-free anaesthesia, we suggest that anaesthetists should reconsider their intra-operative opioid choices on a case-by-case basis.

Correspondence to: E. Albrecht
Email: eric.albrecht@chuv.ch
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Twitter: @DrEAlbrecht; @DrKyleKirkham
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Introduction

Peri-operative opioid administration has long been one of the three pillars of 'balanced anaesthesia' [1], with implementation in practice addressing the dual goals of peri-operative pain relief and pre-emptive analgesia. According to the International Association for the Study of Pain, pain is defined as '*an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage*' [2]. Pain during anaesthesia is typically interpreted through

assessment of surrogate signs such as the response by the sympathetic nervous system to surgical stimuli. This approach is seen also in the peri-operative opioid efficacy literature, which has relied heavily on changes in haemodynamic variables to evaluate intra-operative analgesia [3, 4]. However, the contribution of emotional experience during a state of unconsciousness is questionable, and haemodynamic changes are prone to confounding from a range of physiological processes. The assumption that it is necessary to treat such surrogates with opioids during general anaesthesia may therefore be poorly justified. The approach of providing pre-emptive analgesia, through opioid administration before surgery starts, has been promoted as a strategy to reduce postoperative pain; it is suggested that preventing spinal cord neurons from reaching a state of hyperexcitability will have sustained benefit in the postoperative period [5]. However, although the concept of central sensitisation has been reported in the basic science literature, its clinical relevance has since been disputed by numerous authors [6, 7]. Recently, a meta-analysis of 20 randomised controlled trials and 1343 patients emphasised that there was uncertainty whether pre-emptive opioids result in postoperative pain reduction [8].

Opioid administration is not without concern and is associated with many side-effects such as constipation, urinary retention, respiratory depression and postoperative nausea and vomiting [9]. This last-named outcome in particular is responsible for delayed patient recovery, prolonged patient stay in the recovery area, delayed hospital discharge and unanticipated admission to hospital, all of which increase health service costs [10]. Peri-operative opioid administration is also known to predispose to persistent opioid use, with its concomitant contribution to the current world-wide opioid epidemic [11].

Thus, although peri-operative opioid administration is a long-standing and established custom, it is questionable whether it is appropriate or necessary in contemporary practice. We therefore undertook this meta-analysis to investigate whether opioid-inclusive, compared with opioid-free anaesthesia would reduce postoperative pain, without increasing the rate of postoperative nausea and vomiting.

Methods

This investigation was conducted following the 'Preferred Reporting Items for Systematic Reviews and Meta-Analyses' statement recommended process [12]. The protocol was registered on PROSPERO (registration number: CRD42018100018). The electronic databases Medline and PubMed were searched until June 2018, and the following population search terms were applied: Pain OR Pain measurement OR Pain perception OR Nociception OR Hyperalgesia OR Analgesia. The results of this search were combined with Surgery OR Surgical procedures OR Perioperative period OR Perioperative care. The limits of Clinical trials OR Random allocation OR Therapeutic use were then applied to the results. The following words were searched as keywords: Allodynia*, Pain*, Analgesi*, Nociception*, Surger*, Surgical*, Operation*, Operative*, Perioperati*, Anesthe*, Anaesthe*, Incisi* and Invasive*. The results of this search strategy were limited to randomised controlled trials and humans. No age or language limits were placed on the search. Finally, the references of all articles retrieved from the search were manually reviewed and Google Scholar™ was queried for any relevant trials not already identified using the strategy described above.

The meta-analysis addresses men and women undergoing any surgical operation. Only trials investigating pain outcomes, and comparing any type of intra-operative opioid administration with placebo injection or absence of opioids, were included in the present meta-analysis. In publications where different doses were investigated within the intra-operative opioid regimen, we selected data from the group with the highest dose for analysis. The outcomes extracted from the retrieved articles were derived following our routine approach, described within our previous meta-analyses on acute postoperative pain [13,14] and postoperative nausea and vomiting [15]. The primary outcome was pain score at rest at two postoperative hours. Secondary outcomes related to acute pain included: pain score at rest at 12 and 24 postoperative hours; intravenous (i.v.) morphine consumption equivalents at 2 h, 12 h and 24 h postoperatively; and wound mechanical hyperalgesia threshold. We also aimed to capture the rates of postoperative nausea and vomiting within the first 24 h postoperatively; and hospital resource-related outcomes including length of stay in the recovery area and total hospital length of stay. Extracted trial characteristics included: the type of surgery; intra-operative opioid regimen; medication used for anaesthetic maintenance; and type of postoperative analgesia. The Cochrane Collaboration's Risk of Bias Tool for randomised controlled trials was employed to assess the methodologic quality of each randomised trial [16]. Two authors (JF and AJG) independently screened, reviewed and scored the items for each trial using this method and extracted the relevant data for the analyses. Disagreements with scoring or extracted data were resolved through discussion with a third author (KRK).

Standard deviations, standard errors of mean, 95%CI, number of events and total number of participants were extracted from the source study text, tables or graphs. For trials that did not report the sample size or results as mean (SD), standard error of the mean or 95%CI, the authors were requested twice by mail to provide the missing items or raw trial data. If the requested data were not available, the median and interquartile range were substituted as approximations for the mean and standard deviation, with the mean estimated as equivalent to the median and the standard deviation approximated to be the interquartile range divided by 1.35, or the range divided by 4 [17]. All opioids were converted into equianalgesic doses of i.v. morphine for analysis (i.v. morphine 10 mg = oral morphine 30 mg = i.v. hydromorphone 1.5 mg = oral hydromorphone 7.5 mg = i.v. pethidine 75 mg = oral oxycodone 20 mg = i.v. tramadol 100 mg) [18, 19]. Pain scores reported as visual, verbal or numeric rating scales were converted to a standardised 0–10 analogue scale for quantitative evaluations. Finally, we applied the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group system in order to rate the quality of evidence for each outcome [20]. The GRADE system takes into account: study biases (limitations); the degree of heterogeneity among trials (inconsistency); the presence of a constant definition of the primary outcome (indirectness); and whether the clinical decision would depend on whether the upper or lower boundary limit of the confidence interval represented the truth.

Meta-analyses were conducted using the Review Manager software (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). This tool allows an estimate of the weighted mean differences in continuous data, weighted standardised mean difference for ordinal data and risk ratio for categorical data between groups, with an overall estimate of the pooled effect. We conducted a meta-analysis only when the outcome of interest was reported by two or more trials. The coefficient I^2 was calculated to evaluate heterogeneity, with pre-determined thresholds defined for low (25–49%), moderate (50–74%) and high (> 75%) levels [21]. In cases of moderate or high heterogeneity, a random effects model was applied; otherwise a fixed effect model was employed [22]. A sensitivity analysis was performed on the primary outcome after excluding trials with high or unclear risk of performance bias. Sub-group analysis was applied to all pain-related outcomes according to the type of intra-operative opioid regimen (remifentanil vs. other opioids such as alfentanil, sufentanil, fentanyl), to the type of medication used for anaesthetic maintenance (volatile anaesthetic vs. propofol) and type of surgery (gynaecological surgery vs. abdominal surgery vs. other operations) in an attempt to account for anticipated heterogeneity [22]. The likelihood of publication bias for our primary outcome was assessed by drawing a funnel plot of the mean difference standard error of pain score at rest on postoperative day 1 (y-axis) as a function of the mean difference of pain score at rest on postoperative day 1 (x-axis) [23] and confirmed with Duval and Tweedie's trim and fill test [24]. This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat, Englewood, NJ, USA). A two-sided p value < 0.05 was considered significant.

Results

Of the 4548 trials identified by our literature search, 23 met the inclusion criteria, representing a total of 1304 patients (Fig. 1) [25–47]. For two articles that investigated different types of intra-operative opioids [30, 42], we elected to include data from all groups for analysis. Application of the Cochrane Collaboration Risk of Bias tool (Fig. 2) suggested that the majority of trials had a low risk of bias. Attempts

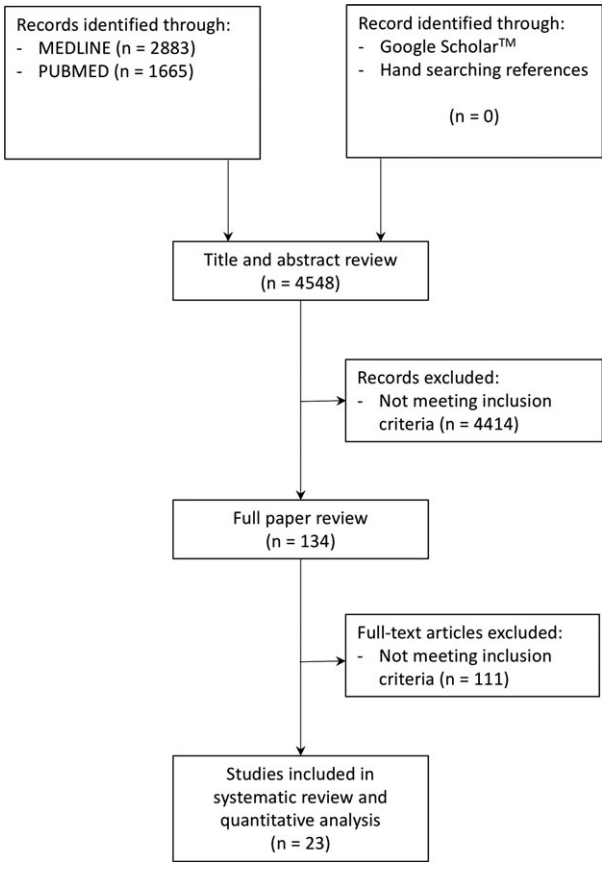

Figure 1 PRISMA flow diagram showing literature search results. Twenty-three randomised controlled trials were included in the analysis.

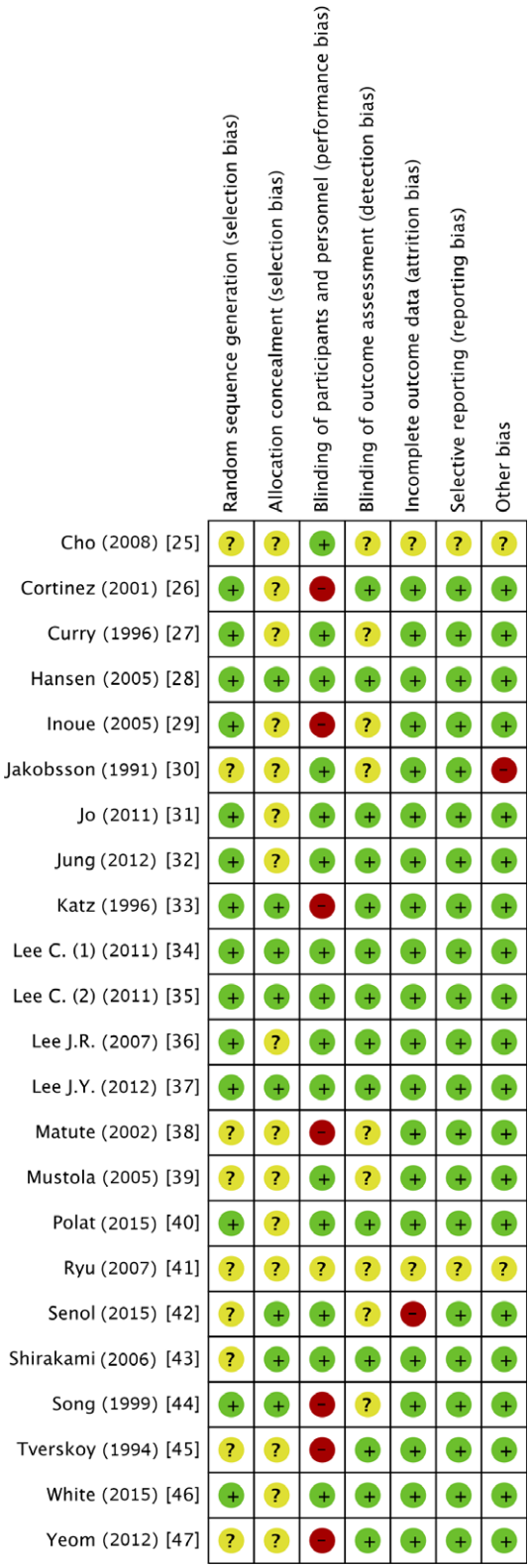

Figure 2 Risk of bias summary of included trials: evaluation of bias risk items for each included study. Green circle, low risk of bias; red circle, high risk of bias; yellow circle, unclear risk of bias.

were made to contact two authors [26, 45]; neither provided the additional data that we requested.

Table 1 presents the trial characteristics. Fourteen trials investigated remifentanil as an intra-operative opioid regimen [25, 26, 28, 31, 32, 34–36, 38–41, 44, 47], five explored fentanyl [27, 29, 43, 45, 46], one alfentanil [33] and one sufentanil [37]; one trial compared fentanyl and alfentanil to a control group [30], and another, remifentanil, alfentanil and morphine to a control group [42]. All included trials administered volatile anaesthetics to maintain anaesthesia except five that administered propofol [27, 30, 31, 36, 39]. Regarding the types of surgery, authors included patients scheduled for gynaecological surgery in eight trials [25–27, 31, 33, 37, 44, 45]; patients undergoing abdominal surgery in six trials [28, 35, 36, 38, 41, 42]; and finally, we combined the remaining nine trials together into an 'other surgery' group [29, 30, 32, 34, 39, 40, 43, 46, 47].

Mean pain scores (95%CI) at rest at two postoperative hours were 3.6 (2.7–4.5) and 3.4 (2.5–4.4) in the opioid-inclusive and opioid-free groups, respectively, with a mean difference of −0.2 (−0.5 to 0.2), p = 0.38, and with sub-group differences observed between intra-operative opioid regimens, p = 0.01 (Fig. 3). A sensitivity analysis was conducted after excluding trials with high risk of performance bias, which revealed a similar mean difference (95%CI) of −0.3 (−0.7 to 0.01), I^2 = 84%, p for overall effect = 0.11, p for sub-group difference = 0.007. Sub-group analyses according to maintenance anaesthetics or type of surgery did not reveal any differences between groups (see also Supporting Information Table S1). With regard to the funnel plot for our primary outcome, the Duval and Tweedie's trim and fill test revealed the point estimates for the combined studies to be 0.22 (95%CI: −0.37 to 0.07); using Trim and Fill, these values are unchanged, suggesting that no trial is missing from publication. The quality of evidence for our primary outcome was high according to the GRADE system. Secondary acute pain-related outcomes were not different between groups (see also Supplementary Information Table S1). Indeed, mean differences (95%CI) in pain scores at rest at 12 and 24 postoperative hours were 0.1 (−0.5 to 0.7), p = 0.79 and 0.0 (−0.2 to 0.2), p = 0.93, respectively, whereas mean differences (95%CI) in i.v. morphine consumption equivalents were 0.1 (−0.3 to 0.5) mg at two postoperative hours (p = 0.68), 0.4 (−1.1 to 1.9) mg at 12 postoperative hours (p = 0.60) and 0.9 (−1.1 to 2.9) mg at 24 postoperative hours (p = 0.36), respectively. Only one trial investigated wound mechanical hyperalgesia threshold and concluded that peri-operative administration of opioids increases wound mechanical hyperalgesia threshold at 24

Table 1 Trial characteristics.

Reference	Group (n)	Surgery	Opioid regimen		Anaesthetic maintenance	Postoperative analgesia	Primary outcome
			Control	Opioid			
Cho et al., [25]	Opioid free (20) Opioid inclusive (20)	Gynaecological surgery	Normal saline	Remifentanil 3 ng.ml^{-1} (TCI)	Sevoflurane	I.v. PCA of morphine	Not specified
Cortinez et al., [26]	Opioid free (30) Opioid inclusive (30)	Gynaecological surgery	None	Remifentanil 0.25 μg.kg^{-1}.min^{-1} with increments of 0.05–0.1 μg.kg^{-1}.min^{-1} (continuous infusion)	Sevoflurane	I.v. PCA of morphine	Morphine consumption at 24 postoperative hours
Curry et al., [27]	Opioid free (22) Opioid inclusive (22)	Laparoscopic tubal sterilisation	Normal saline	Fentanyl 1 μg.kg^{-1} (bolus)	Propofol	I.v. PCA of fentanyl	Not specified
Hansen et al., [28]	Opioid free (18) Opioid inclusive (21)	Major abdominal surgery	Normal saline	Remifentanil 0.4 μg.kg^{-1}.min^{-1} (continuous infusion)	Sevoflurane	Continuous epidural infusion of bupivacaine + i.v. PCA of morphine	Morphine consumption at 24 postoperative hours
Inoue et al., [29]	Opioid free (25) Opioid inclusive (25)	Cervical spine surgery	None	Fentanyl 100 μg, followed by intermittent 50 μg boluses	Sevoflurane	Flurbiprofen + i.m. fentanyl	Not specified
Jakobsson et al., [30]	Opioid free (44) Opioid inclusive, fentanyl (60) Opioid inclusive, alfentanil (60)	Termination of pregnancy	Normal saline	Fentanyl 100 μg OR alfentanil 500 μg (bolus)	Propofol	Paracetamol and diclofenac	Not specified
Jo et al., [31]	Opioid free (20) Opioid inclusive (20)	Total abdominal hysterectomy	Normal saline	Remifentanil 3–4 ng.ml^{-1} (TCI)	Propofol	I.v. PCA of fentanyl	Not specified
Jung et al., [32]	Opioid free (15) Opioid inclusive (15)	Total knee arthroplasty	Normal saline	Remifentanil 2 ng.ml^{-1} (TCI)	Sevoflurane	Not specified	Maximum systolic arterial pressure
Katz et al., [33]	Opioid free (15) Opioid inclusive (15)	Total abdominal hysterectomy	None	Alfentanil 100 μg.kg^{-1}, f ollowed by a continuous infusion of 1–2 μg.kg^{-1}.min^{-1}	Isoflurane	I.v. PCA of morphine	Not specified

(continued)

Table 1 (*continued*)

Reference	Group (n)	Surgery	Opioid regimen		Anaesthetic maintenance	Postoperative analgesia	Primary outcome
			Control	Opioid			
Lee C et al. (1), [34]	Opioid free (30) Opioid inclusive (30)	Tonsillectomy	Normal saline	Remifentanil 1 $\mu g.kg^{-1}$ followed by a continuous infusion of 0.1 $\mu g.kg^{-1}.min^{-1}$ with increments of 0.05 $\mu g.kg^{-1}.min^{-1}$	Sevoflurane	Pethidine, ketorolac	Time to first postoperative analgesic request
Lee C et al. (2), [35]	Opioid free (25) Opioid inclusive (25)	Laparoscopic prostatectomy	Normal saline	Remifentanil 0.3 $\mu g.kg^{-1}.min^{-1}$ with increments of 0.05 $\mu g.kg^{-1}.min^{-1}$ (continuous infusion)	Desflurane	I.v. PCA of morphine and ketorolac	Time to first postoperative analgesic request
Lee JR et al., [36]	Opioid free (31) Opioid inclusive (31)	General surgery	Normal saline	Remifentanil 6 $ng.ml^{-1}$ (TCI)	Propofol	Not specified	Not specified
Lee JY et al., [37]	Opioid free (25) Opioid inclusive (28)	Laparoscopic hysterectomy	Normal saline	Sufentanil 0.3 $\mu g.kg^{-1}.h^{-1}$ (continuous infusion)	Desflurane	I.v. PCA of fentanyl, hydromorphone and ketorolac	Not specified
Matute et al., [38]	Opioid free (60) Opioid inclusive (53)	Major thoracic or abdominal surgery	None	Remifentanil 2 $\mu g.kg^{-1}$ followed by a continuous infusion of 0.1–1 $\mu g.kg^{-1}.min^{-1}$	Sevoflurane	Continuous epidural infusion of bupivacaine + fentanyl	Need for rescue analgesic
Mustola et al., [39]	Opioid free (15) Opioid inclusive (15)	Not specified	Normal saline	Remifentanil 5 $\mu g.kg^{-1}.min^{-1}$ (continuous infusion)	Propofol	Not specified	Not specified
Polat et al., [40]	Opioid free (30) Opioid inclusive (30)	Nasal surgery	Normal saline	Remifentanil 0.05 $\mu g.kg^{-1}.min^{-1}$ (continuous infusion)	Desflurane	I.v. boluses of fentanyl	Sedation score
Ryu et al., [41]	Opioid free (30) Opioid inclusive (30)	Gastrectomy	Normal saline	Remifentanil 1 $ng.ml^{-1}$ (TCI)	Sevoflurane	Not specified	Not specified

(continued)

Table 1 (*continued*)

Reference	Group (n)	Surgery	Opioid regimen		Anaesthetic maintenance	Postoperative analgesia	Primary outcome
			Control	Opioid			
Senol Karatas et al., [42]	Opioid free (16) Opioid inclusive, remifentanil (16) Opioid inclusive, alfentanil (16) Opioid inclusive, morphine (16)	Major abdominal surgery	Normal saline	Remifentanil 1 $\mu g.kg^{-1}$ followed by a continuous infusion of 0.25 $\mu g.kg^{-1}.min^{-1}$ OR alfentanil 10 $\mu g.kg^{-1}$, followed by a continuous infusion of 0.5 $\mu g.kg^{-1}.min^{-1}$ OR morphine 0.1 $mg.kg^{-1}$ followed by a continuous infusion of 0.02 $mg.kg^{-1}.h^{-1}$	Desflurane	I.v. PCA of meperidine	Meperidine consumption at 48 postoperative hours
Shirakami et al., [43]	Opioid free (26) Opioid inclusive (25)	Breast cancer surgery	Normal saline	Fentanyl 25 μg, 4 boluses	Sevoflurane	I.v. flurbiprofen, loxoprofen, teprenone	Not specified
Song et al., [44]	Opioid free (22) Opioid inclusive (24)	Laparoscopic tubal ligation	None	Remifentanil 0.05–0.2 $\mu g.kg^{-1}.min^{-1}$ (continuous infusion)	Desflurane	Ketorolac	Not specified
Tverskoy et al., [45]	Opioid free (9) Opioid inclusive (9)	Transabdominal hysterectomy	None	Fentanyl 5 $\mu g.kg^{-1}$ followed by a continuous infusion of 0.02 $\mu g.kg^{-1}.min^{-1}$	Isoflurane	Meperidine, dipyrone	Not specified
White et al., [46]	Opioid free (50) Opioid inclusive (50)	Superficial outpatient surgery	Normal saline	Fentanyl 100 μg (bolus)	Desflurane	Hydrocodone, i.v. hydromorphone	Not specified
Yeom et al., [47]	Opioid free (20) Opioid inclusive (20)	Posterior lumbar spinal fusion	None	Remifentanil 0.03 $\mu g.kg^{-1}.min^{-1}$ (continuous infusion)	Sevoflurane	I.v. PCA of fentanyl	Fentanyl consumption at 48 postoperative hours

i.m., intramuscular; i.v., intravenous; PCA, patient-controlled analgesia; TCI, target-controlled infusion.

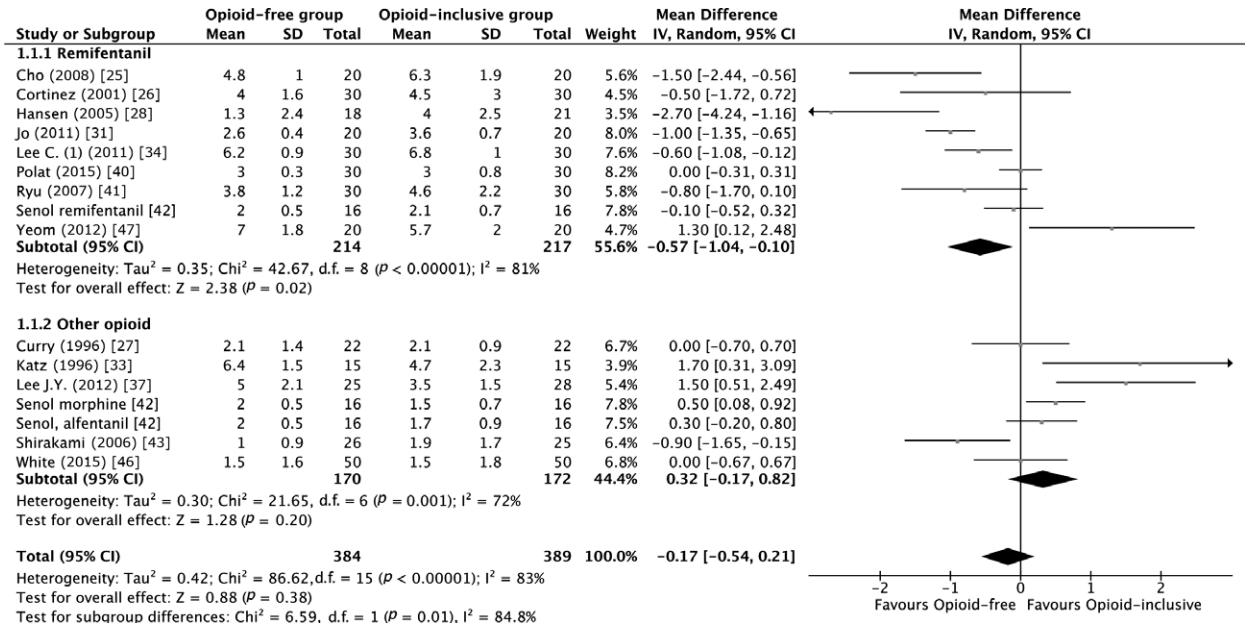

Figure 3 Pain score at rest at two postoperative hours according to the type of intra-operative opioid regimen (remifentanil vs. other opioid).

postoperative hours with a mean difference (95%CI) to pressure of 0.5 (0.2–0.8) kg, I^2 n/a, p = 0.003 [45].

The rate of postoperative nausea and vomiting within the first 24 postoperative hours was recorded by 14 trials [25–27, 29–31, 35, 36, 40, 42–44, 46, 47], and was 24% and 19% in the opioid-inclusive and opioid-free groups, respectively. The risk ratio (95%CI) for this outcome was 0.77 (0.61–0.97), I^2 = 16%, p = 0.03. Finally, length of stay in the recovery area was investigated by six trials [27, 30, 40, 43, 44, 46] and was similar between groups, with a mean difference (95%CI) of 0.6 min (−8.2 to 9.3), I^2 = 60%, p = 0.90. No trials reported hospital length of stay.

Table 2 summarises the findings according to the GRADE system.

Discussion

This systematic review and meta-analysis investigated the effect of opioid-inclusive, compared with opioid-free, anaesthesia on postoperative pain and the rate of postoperative nausea and vomiting. Based on 23 randomised controlled trials, including a total of 1304 patients, we demonstrated that both anaesthetic strategies resulted in similar analgesia in the immediate postoperative period, and for up to 24 postoperative hours. In sub-group analysis of remifentanil as the comparator, the mean pain score difference of 0.6 at two postoperative hours favouring the opioid-free group, is statistically significant but in our view, clinically negligible. This is especially true when considering that subsequent analyses at other time intervals do not support any difference. Likewise, for patients receiving opioids other than remifentanil, the mean opioid consumption difference at two postoperative hours of 1 mg of i.v. morphine equivalent favouring opioid-inclusive anaesthesia does not have any clinical relevance. There was similarly no evidence of a difference at subsequent time intervals.

Our investigation explores the impact of intra-operative opioids on peri-operative analgesia. One mechanism whereby postoperative pain management may be compromised is opioid-induced hyperalgesia, a phenomenon describing enhanced sensitivity to pain stimuli in patients receiving opioids. Two systematic reviews [48, 49] and one meta-analysis [50] have previously explored whether opioid-inclusive anaesthesia may be associated with opioid-induced hyperalgesia. Among the three papers, one review was inconclusive [49], another did not conduct any quantitative analyses [48] and the third was prone to many limitations [50]. Indeed, authors of this last-named meta-analysis included articles with patients under general or regional anaesthesia, and articles that compared patients who received high doses of opioids with those who received low doses or no opioids [50]. Among the trials meeting our inclusion criteria, only one specifically investigated wound mechanical hyperalgesia threshold, with the conclusion that peri-operative administration of fentanyl was associated with opioid-induced hyperalgesia [45]. As we were unable to

Table 2 Summary of findings.

Quality assessment						Summary of findings		
Outcome	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Total number of participants**	**Conclusion**	**Quality of evidence (GRADE)**
Pain score at rest at two postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	773	Equivalent pain scores in both groups	High quality (⊕⊕⊕⊕)[e]
Pain score at rest at 12 postoperative hours (analogue scale, 0–10)	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	286	Equivalent pain scores in both groups	High quality (⊕⊕⊕⊕)[e]
Pain score at rest 24 postoperative hours (analogue scale, 0–10)	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	587	Equivalent pain scores in both groups	High quality (⊕⊕⊕⊕)
Intravenous morphine consumption equivalents at two postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	443	Equivalent con sumption in both groups	High quality (⊕⊕⊕⊕)[e]
Intravenous morphine consumption equivalents at 12 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	216	Equivalent consumption in both groups	High quality (⊕⊕⊕⊕)[e]
Intravenous morphine consumption equivalents at 24 postoperative hours	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	295	Equivalent consumption in both groups	High quality (⊕⊕⊕⊕)[e]
Wound mechanical hyperalgesia threshold	Outcome reported by a single study	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	-	18	Increased threshold in opioid-inclusive group	Very low quality (⊕OOO)[f]
Rates of postoperative nausea and vomiting within the first 24 postoperative hours	No major limitations[a]	No serious inconsistency	No serious indirectness[c]	No serious imprecision[d]	No publication bias	947	Less postoperative nausea and vomiting in opioid-free group	High quality (⊕⊕⊕⊕)[e]
Length of stay in recovery area	No major limitations[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	No publication bias	509	Equivalent length of stay in both groups	High quality (⊕⊕⊕⊕)[e]

[a]Even if allocation concealment was not clear in a majority of studies, we estimate that this does not represent a major limitations after reviewing the global risk biases assessment.
[b]I^2 above 50% or not applicable as only one trial reported this outcome.
[c]Consistent definition of the reported outcome.
[d]No serious imprecision as the clinical decision would not be modified whether the upper of lower boundary limit of the confidence interval represented the truth.
[e]Although there was a concern about inconsistency, we did not further rate down the quality of evidence because not every criterion appeared to justify rating down by one level. Moreover, there was consistent evidence, from randomised controlled trials, with no plausible confounders.
[f]We rated down for limitations and inconsistency, as only one trial reported this outcome.

conduct an analysis of this outcome and to comment on this specific phenomenon, we have presented the quality of evidence as low. Although the possible association between postoperative hyperalgesia and peri-operative administration of high- vs. low-dose opioids was not the objective of this meta-analysis, we have demonstrated that opioid-inclusive anaesthesia does not offer an evident advantage over an opioid-free strategy for postoperative pain outcomes. This finding calls into question the practice of using opioids to treat increases in haemodynamic values during surgery as surrogates of peri-operative pain. Recently, Scott et al. demonstrated, in a prospective clinical model, that infusion of propofol alone produces loss of response to painful stimuli but at a higher plasma concentration than when propofol is combined with remifentanil [51]. This is therefore just one option available among the host of multi-modal agents to help achieve opioid-free anaesthesia, including alpha-2 agonists, ketamine, magnesium, dexamethasone and esmolol [9, 52]. Furthermore, in many situations regional techniques, such as the transvsersus abdominis plane block, can also reduce postoperative opioid consumption [53]. Each option permits individualisation of the anaesthetic strategy based on a case-by-case situation.

In addition to our primary finding, opioid-free anaesthesia was associated with a 20% reduction in postoperative nausea and vomiting. This result highlights that the risk factors for postoperative nausea and vomiting include not only postoperative opioid use [10], but also intra-operative administration. Although postoperative nausea and vomiting is typically considered an unfortunate but inherent effect of opioid-based analgesia, it has been shown that vomiting is ranked highest by patients in outcomes to avoid, ahead of postoperative pain and all other outcomes measured [54]. The presence of postoperative nausea and vomiting is stressful for patients and responsible for system resource consumption including delayed recovery, prolonged length of stay in both recovery area and hospital, unanticipated admission and finally, increased costs of health service [10]. We therefore believe that an opioid-free anaesthetic regimen represents a major advantage and should be considered, especially in at-risk patients, among the strategies to prevent postoperative nausea and vomiting [10].

There are notable limitations to this meta-analysis. First, nearly 60% of the included trials investigated remifentanil. Due to its ultra-short duration of action, an analgesic effect might not be expected postoperatively, even immediately after emergence. Despite this weighting of reports to a single analgaesic, we have attempted to explore this factor by performing sub-group analysis where appropriate. Second, although we attempted to group trials according to the intra-operative opioid regimen, medication used for anaesthetic maintenance (volatile anaesthetic vs. propofol), or surgery type, the coefficient of heterogeneity (I^2) remained high and despite the inclusion of secondary outcome sub-group analyses, we suggest caution with definitive conclusions. Although we feel that our meta-analysis provides the strongest evidence given the current literature, the high heterogeneity coefficients imply that a large randomised controlled trial investigating opioids other than remifentanil would be a valuable addition [23]. Finally, apart from length of stay in the recovery area, we were unable to draw any robust conclusion regarding the impact of an opioid-free anaesthesia on hospital resource-related outcomes. Consequently, the existing literature would benefit from additional trials employing consistent methodology to explore these peri-operative outcomes.

In conclusion, there is high-quality evidence that opioid-inclusive anaesthesia, when compared with opioid-free anaesthesia, does not reduce the level of pain or opioid consumption in the postoperative period, but is associated with increased postoperative nausea and vomiting. We believe these results will help anaesthetists individualise an anaesthetic strategy on a case-by-case basis. The literature would benefit from additional robust methodological trials to better define the impact of each anaesthetic strategy on health system resources.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Secondary pain-related outcome.