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REVIEW

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Low- versus high-dose intraoperative opioids: A systematic review with meta-analyses and trial sequential analyses

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Background: Opioid-induced hyperalgesia is a state of nociceptive sensitisation secondary to opioid administration. The objective of this meta-analysis was to test the hypothesis that high-dose intraoperative opioids contribute to increased post-operative pain and hyperalgesia when compared with a low-dose regimen in patients under general anaesthesia.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines and rated the certainty of evidence with the Grading of Recommendations, Assessment, Development and Evaluation system. Only trials investigating pain outcomes and comparing two different dosages of the same intraoperative opioid in patients under general anaesthesia were included. The primary outcome was pain score (analogue scale, 0-10) at 24 post-operative hours. Secondary outcomes included pain score and cumulative intravenous morphine equivalents (mg) consumed at 2 post-operative hours, together with mechanical pain threshold ($g{\cdot}mm^{-2}$).

Results: Twenty-seven randomised controlled trials, including 1630 patients, were identified. Pain score at rest at 24 post-operative hours was increased in the high-dose group (mean difference [95% CI]: −0.2 [−0.4, −0.1]; trial sequential analysis-adjusted CI: −0.4, −0.02; low certainty of evidence). Similarly, at 2 post-operative hours, both pain score (mean difference [95% CI]: −0.4 [−0.6, −0.2]; low certainty of evidence) and cumulative intravenous morphine equivalents consumed (mean difference [95% CI]: −1.6 mg [−2.6, −0.7]; low certainty of evidence) were significantly higher in the high-dose group. Finally, the threshold for mechanical pain was significantly lower in the high-dose group (mean difference to pressure [95% CI]: 3.8 $g{\cdot}mm^{-2}$ [1.8, 5.8]; low certainty of evidence).

Conclusions: There is low certainty of evidence that high-dose intraoperative opioid administration increases pain scores in the post-operative period, when compared with a low-dose regimen.

1 | INTRODUCTION

Opioid-induced hyperalgesia is described as a state of nociceptive sensitisation secondary to opioid administration.[1] The phenomenon, first reported during 1870 in the setting of morphine administration,[2] has been observed in both animals and humans and associated with virtually all opioids, including fentanyl,[3] alfentanil,[4] sufentanil,[5] remifentanil[6] and tramadol.[7] The nociceptive sensitisation involves changes at peripheral nerve endings and second-order neurons, among other adaptations, and is related to high-dose administration

of opioids, increased duration of administration and abrupt discontinuation.[8] Indeed, nociceptive sensitisation induced by elevated doses of opioids produces a) modulations from the central glutaminergic system, b) increased spinal dynorphin concentrations, c) activation of pain-facilitation descending pathways from the rostral ventromedial medulla, d) genetic mechanisms and e) decreased reuptake of neurotransmitters including substance P and glutamate from the primary afferent fibres compounded by enhanced spinal neuron response to these same neurotransmitters.[9] Opioid-induced hyperalgesia is characterised by a poorly defined pain that extends from the surgical site, together with diffuse allodynia.[9]

Contemporary perioperative care pursues dual objectives of optimising patient comfort while accelerating clinical recovery, thus using less healthcare resources. In this setting and in the light of the current international opioid consumption epidemic,[10] it is critically important to better understand the implications of perioperative opioid administration, including its impact on post-operative analgesia and opioid consumption. The clinical contribution of opioid-induced hyperalgesia remains unclear despite two systematic reviews that have previously explored the subject, but did not perform quantitative analyses.[8,11] While one paper reported its conclusion based on three randomised controlled trials and five case reports of intravenous opioid administration,[8] the other review concluded that there was insufficient evidence to confirm the existence of opioid-induced hyperalgesia in clinical practice.[11]

We undertook this systematic review, meta-analysis, with trial sequential analysis (TSA) to test the hypothesis that high-dose intraoperative opioids increase post-operative pain and hyperalgesia when compared with a low-dose regimen in adult patients under general anaesthesia, scheduled for any type of surgical operation.

Editorial Comment

Post-operative hyperalgesia related to degree of intraoperative opioid exposure is an area of current clinical interest. In this meta-analysis, results show that high-dose opioids, and probably remifentanil, are associated with early post-operative hyperalgesia, though the confidence or certainty for this finding is low because of limitations in available studies.

2 | METHODS

This investigation followed the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" recommended process,[12] and the protocol was registered with PROSPERO (registration number: CRD42018105049). We followed a standard methodology that has been described previously in meta-analyses on acute post-operative pain that includes registration of the protocol, literature search, definition of population-intervention-comparator-outcomes, selection of RCTs, data extraction, and statistical analyses.[13-15] We also followed the approach recommended to increase the validity of meta-analyses[16]; this approach contains eight different steps that are briefly described in Table S1.

2.1 | Literature search and inclusion criteria

A librarian searched the MEDLINE and EMBASE electronic databases up to 30 June 2019, and applied the following population search terms: Pain OR Pain measurement OR Pain perception OR Nociception OR Hyperalgesia OR Analgesia. These search results were combined with Surgery OR Surgical procedures OR Perioperative period OR Perioperative care. Results were further limited with Clinical trials OR Random allocation OR Therapeutic use. 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. The results of the search strategy were examined by two authors (JF and LK) and disagreements for trial selection were resolved through discussion with the third author (EA). In addition, the references of all articles retrieved from the search were scrutinised for relevant trials not identified using the strategy described above. Finally, Google Scholar™ was examined for any additional appropriate publications.

2.2 | Population

The meta-analysis addresses female and male adults (≥18 years old) undergoing any surgical operation under general anaesthesia but without a regional anaesthetic or local infiltration analgesia technique.

2.3 | Intervention and comparator

Only trials reporting pain outcomes and comparing two different intraoperative dosages of the same opioid were included in the present meta-analysis.

2.4 | Outcomes

The primary outcome was pain score at rest at 24 post-operative hours. Secondary acute pain-related outcomes were pain score at rest at 2 post-operative hours; cumulative intravenous (iv) morphine equivalents consumed up to 2 and 24 hours post-operatively; and mechanical pain threshold ($g{\cdot}mm^{-2}$). We also aimed to capture hospital resources-related outcomes (extubating time, length of stay in the post-anaesthetic care unit, hospital length of stay). Serious adverse events as defined by the ICH-GCP (International Conference on Harmonisation—Good Clinical Practice) were also sought, after request during the reviewing process.

2.5 | Trial characteristics

Extracted trial characteristics included the type of surgery, intraoperative opioid regimen, medication used for anaesthetic maintenance, and type of post-operative analgesia. We also reported the mean dose

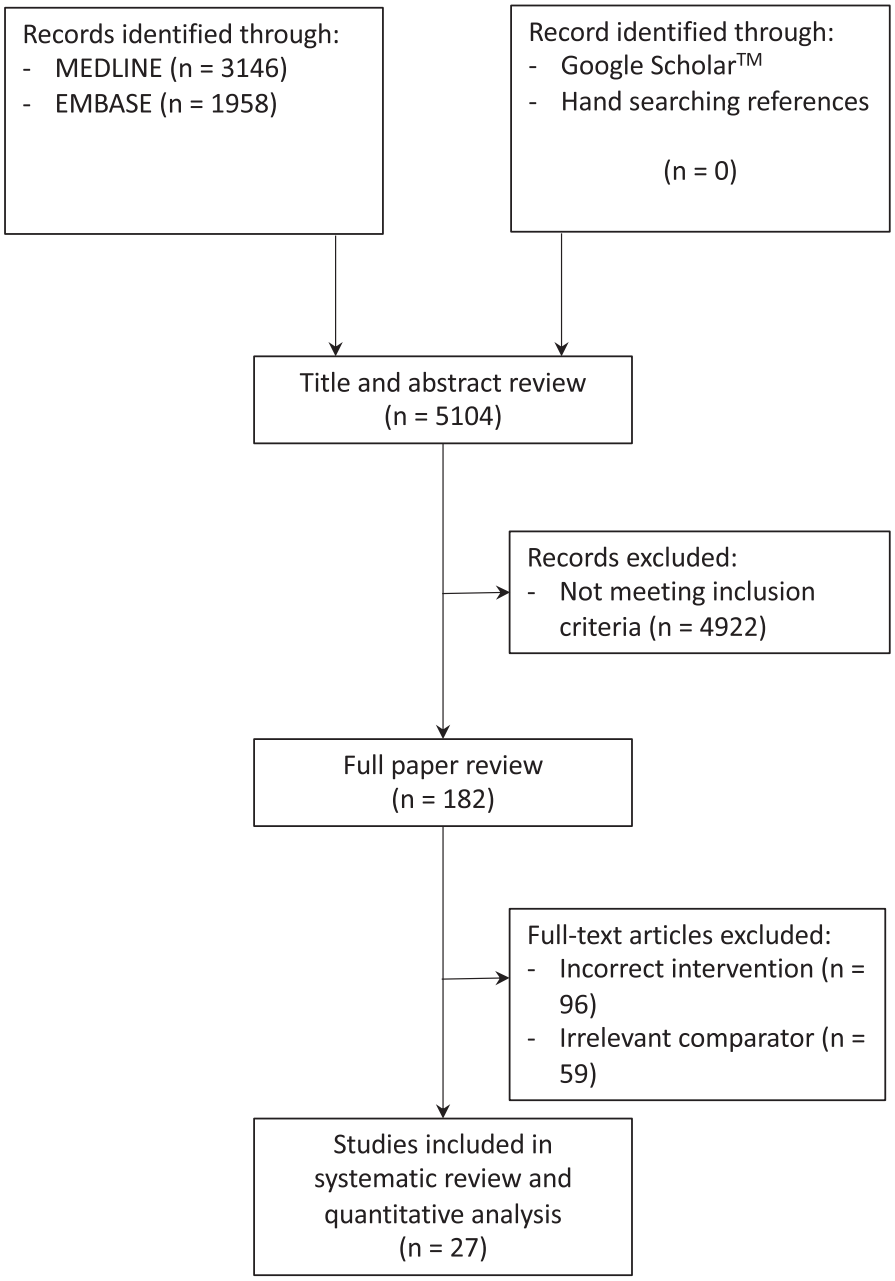

FIGURE 1 PRISMA flow diagram showing literature search results. Twenty-seven randomised controlled trials were included in the analysis. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses

of opioids administered. When not specifically described, the mean dose was calculated from the mean weight and duration of surgery.

2.6 | Data extraction

Two authors (JF and LK) independently extracted data and disagreements were resolved through discussion with the third author (EA). The source article texts, tables or graphs were used to extract means, standard deviations, standard error of means, 95% confidence intervals (CI), number of events and total number of participants. For trials that did not report the sample size or results as a mean and standard deviation or standard error of the mean and 95% CI, authors were contacted twice by mail to request access to the missing or raw data. If no reply was received, the median and interquartile range were used for mean and standard deviation approximations, with the mean estimated to be equivalent to the median and the standard deviation approximated as the interquartile range divided by 1.35, or the range divided by 4.[17] Pain scores reported as Visual, Verbal or Numeric Rating Scales were converted to a standardised 0-10 analogue scale for quantitative evaluations. All opioids were converted into equianalgesic doses of iv morphine (iv morphine 10 mg = oral morphine 30 mg = iv hydromorphone 1.5 mg = oral hydromorphone 7.5 mg = iv pethidine 75 mg = oral oxycodone 20 mg = iv tramadol 100 mg).[18]

2.7 | Risk of bias assessment and quality of evidence

The Cochrane Collaboration's Risk of Bias Tool for randomised controlled trials was applied to evaluate the quality of the research

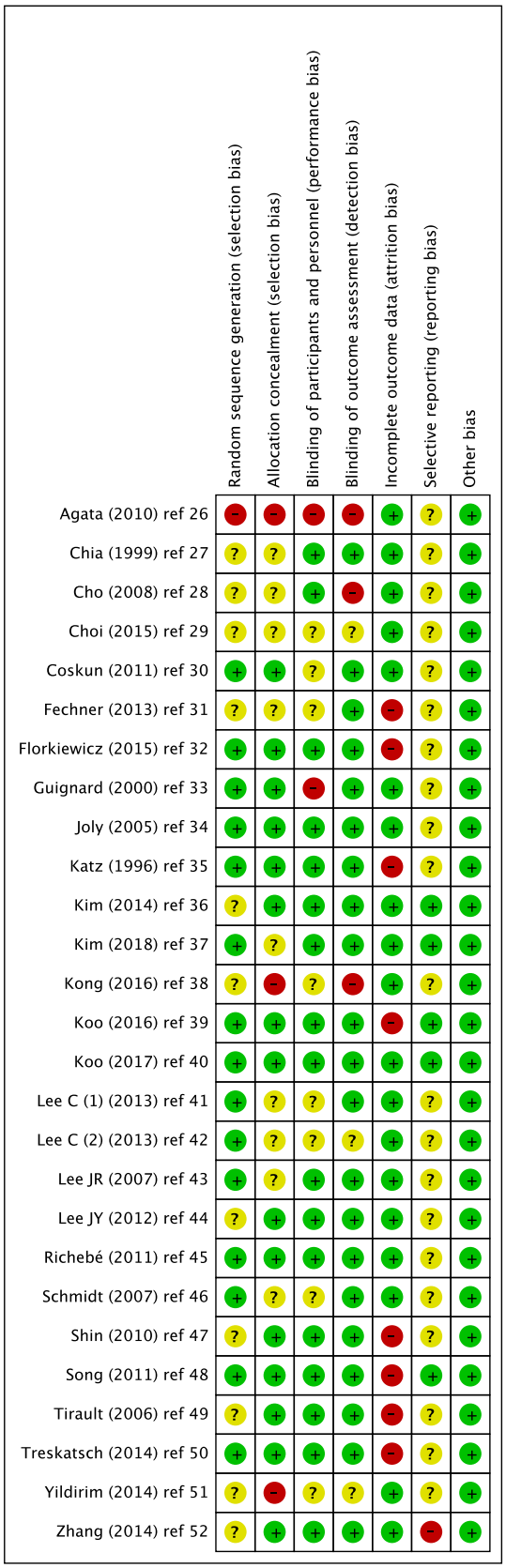

FIGURE 2 Cochrane collaboration risk of bias summary: evaluation of bias risk items for each included study. Green circle represents low risk of bias; red circle represents high risk of bias; yellow circle represents unclear risk of bias [Colour figure can be viewed at wileyonlinelibrary.com]

methodology for each randomised trial.[19] Three authors (JF, LK and SG) independently screened, reviewed and scored the items for each trial using this method and disagreements with scoring were resolved through discussion with the third author (EA). Of note, authors were not contacted for clarifications regarding the unknown risk of biases. Finally, the quality of evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[20]

2.8 | Statistical analysis

Meta-analyses were conducted with Review Manager (RevMan version 5.3.5; Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration 2014). This software estimates the weighted mean differences for 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 if two or more trials reported the relevant outcome. The I^2 coefficient was calculated in order to evaluate heterogeneity with pre-determined thresholds defined for low (25%-49%), moderate (50%-74%) and high (>75%) levels.[21] A random effects model was applied in cases of moderate or high heterogeneity; otherwise a fixed effects model was used. All pain-related outcomes were analysed in subgroups according to the type of intraoperative opioid regimen (remifentanil vs other opioids such as alfentanil, sufentanil, fentanyl, morphine) or post-operative analgesic regimen (inclusive or not of nonsteroidal anti-inflammatory medications or acetaminophen) to account for heterogeneity. Given propofol has been suggested to reduce pain scores by 40%[22] and post-operative pain intensity varies between different types of surgical procedure,[23] we also performed subgroup analyses according to medication used for anaesthetic maintenance (volatile anaesthetic vs propofol) and surgical type (gynaecological surgery vs abdominal surgery vs cardiac surgery vs other surgeries). The likelihood of publication bias within our primary outcome was assessed by drawing a funnel plot of standard error of the mean difference in pain score at rest on post-operative day 1 (y-axis) as a function of the mean difference in pain score at rest on post-operative day 1 (x-axis) and confirmed with Duval and Tweedie's trim and fill test.[24] This assessment was performed using Comprehensive Meta-analysis Version 2 software (Biostat). Finally, a TSA was executed on all outcomes to confirm whether firm evidence was reached or not (TSA software version 0.9.5.10 Beta; Copenhagen Trial Unit, Center for Clinical Intervention Research, Rigshospitalet).[25] If necessary, a post-hoc analysis was performed. Results are presented as the mean difference or relative risk with 95% CI. A two-sided P value < .033 was considered significant, based on reviewer suggestions, to account for assessments at two time intervals.[16] However, even if P values are corrected for multiple testing, one should bear in mind that the confidence intervals are directly related to a P-value of .05; therefore P-values of .05 are still indirectly used while considering the confidence intervals for GRADE assessments.

TABLE 1 Trial characteristics

Reference	Group (n)	Surgery	Opioid regimen during maintenance		Anaesthetic maintenance	Post-operative analgesia	Primary outcome
			Low dose	High dose			
Agata et al[26]	Low dose (15) High dose (15)	Maxillofacial surgery	Remifentanil 0.15 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 1800 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 3600 µg)	Sevoflurane	iv PCA fentanyl	Not specified
Chia et al[27]	Low dose (30) High dose (30)	Hysterectomy	Fentanyl 1 $\mu g \cdot kg^{-1}$ (single bolus at the induction; total dose: 56 µg)	Fentanyl 15 $\mu g \cdot kg^{-1}$ (bolus over 20 minutes) followed by 100 $\mu g.h^{-1}$ (total dose: 1060 µg)	Halothane	iv PCA fentanyl	Pain score at 16 post-operative hours
Cho et al[28]	Low dose (20) High dose (20)	Gynaecological surgery	Remifentanil 1 $ng \cdot mL^{-1}$ (TCI) (total dose: 381 µg)	Remifentanil 3 $ng \cdot mL^{-1}$ (TCI) (total dose: 1170 µg)	Sevoflurane	iv PCA morphine	Not specified
Choi et al[29]	Low dose (25) High dose (25)	Gynaecological surgery	Remifentanil 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 376 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 2520 µg)	Desflurane	iv PCA fentanyl	Fentanyl consumption at 48 post-operative hours
Coskun et al[30]	Low dose (23) High dose (23)	Oocyte retrieval	Remifentanil 1.5 $ng \cdot mL^{-1}$ (TCI) (total dose: 108 µg)	Remifentanil 2.5 $ng \cdot mL^{-1}$ (TCI) (total dose: 124 µg)	Propofol	Oral paracetamol	Not specified
Fechner et al[31]	Low dose (20) High dose (22)	Coronary artery bypass graft surgery	Sufentanil 0.4 $ng \cdot mL^{-1}$ (TCI) (total dose: 182 µg)	Sufentanil 0.8 $ng \cdot mL^{-1}$ (TCI) (total dose: 338 µg)	Propofol	iv PCA morphine	Morphine consumption at 48 post-operative hours
Florkiewicz et al[32]	Low dose (43) High dose (47)	Coronary bypass grafting or heart valve surgery	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 1892 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 5248 µg)	Propofol	iv PCA oxycodone	Oxycodone consumption at 48 post-operative hours
Guignard et al[33]	Low dose (25) High dose (24)	Open colorectal surgery	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 1656 µg)	Remifentanil 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with increments of 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 4992 µg)	Desflurane	iv PCA morphine	Morphine consumption at 24 post-operative hours
Joly et al[34]	Low dose (25) High dose (25)	Open colorectal surgery	Remifentanil 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 900 µg)	Remifentanil 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 6700 µg)	Desflurane	iv PCA morphine	Mechanical pain threshold (von Frey filament stimulation)
Katz et al[35]	Low dose (15) High dose (15)	Total abdominal hysterectomy	Alfentanil, boluses of 10-20 $\mu g \cdot kg^{-1}$ every hour (total dose: 3331 µg)	Alfentanil, continuous infusion of 1-2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 17 048 µg)	Isoflurane	iv PCA morphine	Not specified
Kim et al[36]	Low dose (63) High dose (63)	Local breast excision	Remifentanil 5 $ng \cdot mL^{-1}$ (TCI) (total dose: 1013 µg)	Remifentanil 10 $ng \cdot mL^{-1}$ (TCI) (total dose: 1894 µg)	Propofol	Ketorolac	Composite index of nausea, vomiting and itching
Kim et al[37]	Low dose (40) High dose (40)	Gastrectomy	Remifentanil 2 $ng \cdot mL^{-1}$ (TCI) (total dose: 923 µg)	Remifentanil 12 $ng \cdot mL^{-1}$ (TCI) (total dose: 5267 µg)	Sevoflurane	iv PCA fentanyl	Cumulative post-operative fentanyl consumption

(Continues)

TABLE 1 (Continued)

Reference	Group (n)	Surgery	Opioid regimen during maintenance		Anaesthetic maintenance	Post-operative analgesia	Primary outcome
			Low dose	High dose			
Kong et al[38]	Low dose (24) High dose (25)	Laparoscopic cholecystectomy	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 406 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 1077 µg)	Sevoflurane	iv PCA fentanyl	Not specified
Koo et al[39]	Low dose (27) High dose (26)	Pancreaticoduodenectomy	Remifentanil 1 $ng \cdot mL^{-1}$ (TCI) (total dose: 841 µg)	Remifentanil 4 $ng \cdot mL^{-1}$ (TCI) (total dose: 2708 µg)	Sevoflurane	iv PCA morphine	Morphine consumption at 48 post-operative hours
Koo et al[40]	Low dose (30) High dose (31)	Thyroid surgery	Remifentanil 1 $ng \cdot mL^{-1}$ (TCI) (total dose: µg)	Remifentanil 4 $ng \cdot mL^{-1}$ (TCI) (total dose: µg)	Desflurane	im ketorolac	Mechanical pain threshold (von Frey filament stimulation) at 24 post-operative hours
Lee et al (1)[41]	Low dose (30) High dose (29)	Laparoscopic urologic surgery	Remifentanil 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 600 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 3400 µg)	Desflurane	iv PCA morphine and ketorolac	Mechanical pain threshold (von Frey filament stimulation) at 24 post-operative hours
Lee et al (2)[42]	Low dose (28) High dose (29)	Laparoscopic hysterectomy	Remifentanil 0.05 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 413 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 2513 µg)	Desflurane	iv PCA morphine and ketorolac	Mechanical pain threshold (von Frey filament stimulation) at 24 post-operative hours
Lee et al[43]	Low dose (32) High dose (31)	General surgery	Remifentanil 2 $ng \cdot mL^{-1}$ (TCI) (not indicated and unable to calculate)	Remifentanil 6 $ng \cdot mL^{-1}$ (TCI) (not indicated and unable to calculate)	Propofol	Not specified	Not specified
Lee et al[44]	Low dose (28) High dose (28)	Laparoscopic hysterectomy	Sufentanil 0.2 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (total dose: 25 µg)	Sufentanil 0.3 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (total dose: 39 µg)	Desflurane	iv PCA fentanyl, hydromorphone and ketorolac	Not specified
Richebé et al[45]	Low dose (19) High dose (19)	Coronary artery surgery	Remifentanil 7 $ng \cdot mL^{-1}$ (TCI) (total dose: 3661 µg)	Remifentanil 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 5330 µg)	Propofol	iv acetaminophen, iv PCA morphine	Mechanical pain threshold (von Frey filament stimulation) at 44 post-operative hours
Schmidt et al[46]	Low dose (20) High dose (22)	Eye surgery	Remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 562 µg)	Remifentanil 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (total dose: 2131 µg)	Isoflurane	Not specified	Not specified

(Continues)

TABLE 1 (Continued)

Reference	Group (n)	Surgery	Opioid regimen during maintenance		Anaesthetic maintenance	Post-operative analgesia	Primary outcome
			Low dose	High dose			
Shin et al[47]	Low dose (50), propofol High dose (46), propofol	Mastectomy	Remifentanil 1 ng·mL^{-1} (TCI) (total dose: 762 μg)	Remifentanil 4 ng·mL^{-1} (TCI) (total dose: 2064 μg)	Propofol	iv PCA morphine	Morphine consumption at 24 post-operative hours
	Low dose (48), sevoflurane High dose (42), sevoflurane	Mastectomy	Remifentanil 1 ng·mL^{-1} (TCI) (total dose: 870 μg)	Remifentanil 4 ng·mL^{-1} (TCI) (total dose: 2071 μg)	Sevoflurane	iv PCA morphine	Morphine consumption at 24 post-operative hours
Song et al[48]	Low dose (28) High dose (28)	Thyroidectomy	Remifentanil 0.05 μg·kg^{-1}·min^{-1} (total dose: 422 μg)	Remifentanil 0.2 μg·kg^{-1}·min^{-1} (total dose: 1118 μg)	Sevoflurane	iv fentanyl, tramadol, acetaminophen	Mechanical pain threshold (von Frey filament stimulation) at 24 post-operative hours
Tirault et al[49]	Low dose (13) High dose (15)	Major abdominal surgery	Remifentanil 3 ng·mL^{-1} (TCI) (total dose: 1224 μg)	Remifentanil 8 ng·mL^{-1} (TCI) (total dose: 3691 μg)	Propofol	iv PCA morphine	Morphine consumption in phase 1 recovery
Treskatsch et al[50]	Low dose (15) High dose (17)	Intra-abdominal surgery	Remifentanil 0.1 μg·kg^{-1}·min^{-1} (total dose: 1394 μg)	Remifentanil 0.2 μg·kg^{-1}·min^{-1}, with increments of 0.05 μg·kg^{-1}·min^{-1} (total dose: 3040 μg)	Sevoflurane.	iv PCA morphine	Not specified
Yildirim et al[51]	Low dose (50) High dose (50)	Coronary artery surgery	Fentanyl 1-3 μg·kg^{-1}·h^{-1} (total dose: 458 μg)	Fentanyl 5-10 μg·kg^{-1}·h^{-1} (total dose: 1720 μg)	Propofol	iv PCA fentanyl	Not specified
Zhang et al[52]	Low dose (29) High dose (28)	Thyroidectomy	Remifentanil 0.2 μg·kg^{-1}·min^{-1} (total dose: 1067 μg)	Remifentanil 1.2 μg·kg^{-1}·min^{-1} (total dose: 6222 μg)	Propofol	iv morphine infusion if VAS ≥ 4	Not specified

Abbreviations: im, intramuscular; iv, intravenous; PCA, patient-controlled analgesia; TCI, target-controlled infusion.

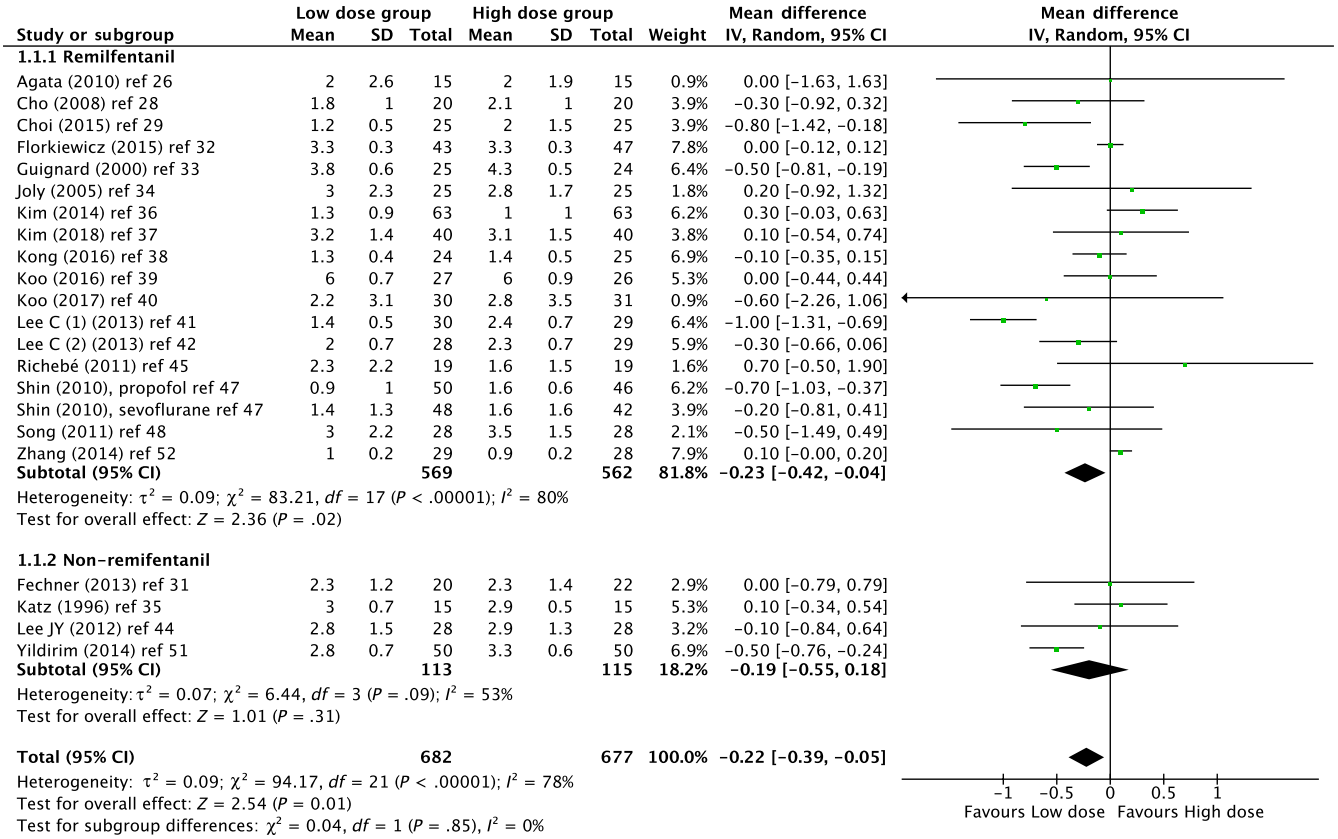

FIGURE 3 Pain score at rest at 24 post-operative hours according to the type of intraoperative opioid regimen (remifentanil vs other opioids) [Colour figure can be viewed at wileyonlinelibrary.com]

3 | RESULTS

Of the 5104 trials identified following our literature search strategy, 27 met the inclusion criteria, representing a total of 1630 patients (Figure 1).[26-52] For one article that investigated two dosages of intraoperative opioids with propofol or sevoflurane intraoperative maintenance,[47] we elected to include data from all groups for analysis. Application of the Cochrane Collaboration Risk of Bias tool (Figure 2) suggested that only one trial had an overall low risk of bias.[40] Attempts were made to contact nine authors and none provided the requested data.[26-28,30,35,39,40,47,48] Reasons behind biases assessment are given in Table S2.

Table 1 presents the trial characteristics. Twenty-two trials investigated remifentanil as an intraoperative opioid regimen,[26,28-30,32-34,36-43,45-50,52] two explored fentanyl,[27,51] two sufentanil[31,44] and one alfentanil.[35] All trials administered opioids before surgical incision. The administered dose ratio between low- and high-dose groups were respectively 1:15 in one trial,[27] between 1:8 and 1:6 in five trials,[29,34,37,41,52] between 1:5 and 1:2 in 18 trials [26,28,31-33,35,36,38-40,42,43,46-51] and at a ratio of 1:1.5 in three trials.[30,44,45] Of note, one trial administered dose that are beyond what is commonly used in the clinical practice.[35] No trials injected long-acting opioids such as morphine or hydromorphone at the end of surgery. Over 60% (18 of 27) of the included trials used a volatile-based anaesthesia maintenance,[26-29,33-35,37-42,44,46,48,50] while the remaining trials administered propofol.[30-32,36,43,45,47,49,51,52] Regarding the types of surgery, authors included patients scheduled for gynaecological surgery in seven trials,[27-30,35,42,44] for abdominal surgery in nine trials,[33,34,37-39,41,43,49,50] for cardiac surgery in four trials,[31,32,45,51] and finally, we combined the remaining seven trials together into an "other surgeries" group.[26,36,40,46-48,52] Five trials included nonsteroidal anti-inflammatory drugs in the post-operative analgesic regimen,[36,40-42,44] and two trials included acetaminophen.[45,48]

Pain scores at rest at 24 post-operative hours were significantly increased in the high-dose group (mean difference [95% CI]: −0.2 [−0.4, −0.1]; I^2 = 78%; P = .01), without any difference observed between intraoperative opioid regimen subgroups (P = .85; random effects model; Figure 3). Similarly, subgroup analyses according to anaesthetic management and type of surgery did not reveal any differences between groups (Table 2).

The TSA indicated that firm evidence was reached regarding the contribution of high-dose of opioids to increased pain scores at 24 post-operative hours, relative to low-dose regimens (Figure 4). After applying a random effects model of *DerSimonian-Laird*, using an alpha value of .05 and beta value of .2, the TSA-adjusted CI was −0.42 to −0.02, P = .01; the inconsistency and diversity coefficients were 78%, and 87% respectively."

TABLE 2 Secondary pain-related outcome

Outcome	Number of trials	References	Total number of patients		Mean difference (95% CI)	TSA-adjusted CI	I^2 (%)	*P* value for overall effect	*P* value for subgroup differences
			Low dose	High dose					
Pain score at rest at 2 post-operative hours (analogue scale, 0-10)									
According to opioid regimen									
Remifentanil	17	Agata et al,[26] Cho et al,[28] Choi et al,[29] Florkiewicz et al,[32] Guignard et al,[33] Kim et al,[36] Kim et al,[37] Kong et al,[38] Koo et al,[39] Koo et al,[40] Lee (1) et al,[41] Lee (2) et al,[42] Schmidt et al,[46] Shin et al,[47] Song et al,[48] Treskatsch et al,[50] Zhang et al[52]	560	557	−0.4 [−0.6, −0.2]		75	<.0001	.96
Other opioids	4	Fechner et al,[31] Katz et al,[35] Lee et al,[44] Yildirim et al[51]	113	115	−0.4 [−1.1, 0.4]		89	.37	
According to anaesthesia maintenance									
Volatile anaesthetic	16	Agata et al,[26] Cho et al,[28] Choi et al,[29] Guignard et al,[33] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Koo et al,[40] Lee (1) et al,[41] Lee (2) et al,[42] Lee et al,[44] Schmidt et al,[46] Shin et al,[47] Song et al,[48] Treskatsch et al[50]	418	416	−0.4 [−0.7, −0.1]		81	.007	.38
Propofol	6	Fechner et al,[31] Florkiewicz et al,[32] Kim et al,[36] Shin et al,[47] Yildirim et al,[51] Zhang et al[52]	255	256	−0.3 [−0.4, −0.1]		70	<.01	
According to type of surgery									
Gynaecological surgery	5	Cho et al,[28] Choi et al,[29] Katz et al,[35] Lee (2) et al,[42] Lee et al[44]	116	117	−0.6 [−1.2, −0.1]		68	.02	.63
Abdominal surgery	6	Guignard et al,[33] Kim et al,[37] Kong et al,[38] Koo et al,[39] Lee (1) et al,[41] Treskatsch et al[50]	161	161	−0.4 [−0.9, 0.1]		88	.15	
Cardiac surgery	3	Fechner et al,[31] Florkiewicz et al,[32] Yildirim et al[51]	113	119	−0.3 [−0.7, 0.2]		78	.20	
Other surgeries	7	Agata et al,[26] Kim et al,[36] Koo et al,[40] Schmidt et al,[46] Shin et al,[47] Song et al,[48] Zhang et al[52]	283	275	−0.3 [−0.5, 0.0]		58	.03	
According to post-operative analgesic regimen									
No NSAID/ Acetaminophen	16	Agata et al,[26] Cho et al,[28] Choi et al,[29] Fechner et al,[31] Florkiewicz et al,[32] Guignard et al,[33] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Schmidt et al,[46] Shin et al,[47] Song et al,[48] Treskatsch et al,[50] Yildirim et al,[51]Zhang et al[52]	494	492	−0.3 [−0.5, −0.2]		81	.0003	.47
Inclusive of NSAID/ Acetaminophen	5	Kim et al,[36] Koo et al,[40]Lee (1) et al,[41] Lee (2) et al,[42] Lee et al[44]	179	180	−0.5 [−1, −0.1]		60	.03	
Total			673	672	−0.4 [−0.6, −0.2]	−0.4, −0.2	78	<.0001	
Pain score at rest at 24 post-operative hours (analogue scale, 0-10)									

(Continues)

TABLE 2 (Continued)

Outcome	Number of trials	References	Total number of patients		Mean difference (95% CI)	TSA-adjusted CI	I^2 (%)	*P* value for overall effect	*P* value for subgroup differences
			Low dose	High dose					
According to anaesthesia maintenance									
Volatile anaesthetic	15	Agata et al,[26] Cho et al,[28] Choi et al,[29] Guignard et al,[33] Joly et al,[34] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Koo et al,[40] Lee (1) et al,[41] Lee (2) et al,[42] Lee et al,[44] Shin et al,[47] Song et al[48]	408	402	−0.3 [−0.5, −0.1]		59	.07	.25
Propofol	7	Fechner et al,[31] Florkiewicz et al,[32] Kim et al,[36] Richebé et al,[45] Shin et al,[47] Yildirim et al,[51] Zhang et al[52]	274	275	−0.1 [−0.4, 0.1]		85	.40	
According to type of surgery									
Gynaecological surgery	5	Cho et al,[28] Choi et al,[29] Katz et al,[35] Lee (2) et al,[42] Lee et al[44]	116	117	−0.3 [−0.5, 0.0]		31	.08	.91
Abdominal surgery	6	Guignard et al,[33] Joly et al,[34] Kim et al,[37] Kong et al,[38] Koo et al,[39] Lee (1) et al[41]	171	169	−0.3 [−0.7, 0.1]		81	.14	
Cardiac surgery	4	Fechner et al,[31] Florkiewicz et al,[32] Richebé et al,[45] Yildirim et al[51]	132	138	−0.1 [−0.5, 0.3]		78	.56	
Other surgeries	6	Agata et al,[26] Kim et al,[36] Koo et al,[40] Shin et al,[47] Song et al,[48] Zhang et al[52]	263	253	−0.2 [−0.5, 0.2]		77	.39	
According to post-operative analgesic regimen									
No NSAID/ Acetaminophen	14	Agata et al,[26] Cho et al,[28] Choi et al,[29] Fechner et al,[31] Florkiewicz et al,[32] Guignard et al,[33] Joly et al,[34] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Shin et al,[47] Yildirim et al,[51] Zhang et al[52]	456	450	−0.2 [−0.4, −0.0]		73	.02	.89
Inclusive of NSAID/ Acetaminophen	7	Kim et al,[36] Koo et al,[40] Lee (1) et al,[41] Lee (2) et al,[42] Lee et al,[44] Richebé et al,[45] Song et al[48]	226	227	−0.2 [−0.4, −0.1]		78	.01	
Total			682	677	−0.2 [−0.4, −0.1]	−0.4, −0.02	78	.01	
Iv morphine consumption equivalents at 2 post-operative hours (mg)									
According to opioid regimen									
Remifentanil	10	Cho et al,[28] Choi et al,[29] Guignard et al,[33] Joly et al,[34] Kim et al,[37] Kong et al,[38] Koo et al,[39] Shin et al,[47] Tirault et al,[49] Treskatsch et al[50]	312	305	−1.9 [−2.8, −1]		88	<.0001	.0001
Other opioids	1	Katz et al[35]	15	15	7.6 [3.1, 12.1]		—	.0008	
According to anaesthesia maintenance									

TABLE 2 (Continued)

Outcome	Number of trials	References	Total number of patients		Mean difference (95% CI)	TSA-adjusted CI	I^2 (%)	*P* value for overall effect	*P* value for subgroup differences
			Low dose	High dose					
Volatile anaesthetic	9	Cho et al,[28] Choi et al,[29] Guignard et al,[33] Joly et al,[34] Kim et al,[37] Kong et al,[38] Koo et al,[39] Shin et al,[47] Treskatsch et al[50]	249	244	−2.3 [−3.6, −1.1]		89	.0002	.38
Propofol	3	Katz et al,[35] Shin et al,[47] Tirault et al[49]	78	76	0.3 [−5.5, 6.1]		89	.91	
According to type of surgery									
Gynaecological surgery	3	Cho et al,[28] Choi et al,[29] Katz et al[35]	60	60	0.2 [−5.4, 5.9]		91	.93	.1
Abdominal surgery	7	Guignard et al,[33] Joly et al,[34] Kim et al,[37] Kong et al,[38] Koo et al,[39] Tirault et al,[49] Treskatsch et al[50]	169	172	−3.8 [−6.4, −1.2]		90	.004	
Cardiac surgery	0	—	—	—	—		—	—	
Other surgeries	1	Shin et al[47]	98	88	−0.8 [−1.9, 0.4]		91	.20	
According to post-operative analgesic regimen									
No NSAID/ Acetaminophen	11	Cho et al,[28] Choi et al,[29] Guignard et al,[33] Joly et al,[34] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Shin et al,[47] Tirault et al,[49] Treskatsch et al[50]	327	320	−1.6 [−2.6, −0.7]		89	.0007	N/A
Inclusive of NSAID/ Acetaminophen	—		—	—	—		—		
Total			327	320	−1.6 [−2.6, −0.7]	−2,7, −0.5	89	.0007	
Iv morphine consumption equivalents at 24 post-operative hours (mg)									
According to opioid regimen									
Remifentanil	11	Agata et al,[26] Cho et al,[28] Florkiewicz et al,[32] Guignard et al,[33] Kim et al,[37] Kong et al,[38] Koo et al,[39] Lee (2) et al,[42] Shin et al,[47] Tirault 2006,[49] Zhang et al[52]	362	357	−6.2 [−23, 10.6]		100	.47	.17
Other opioids	1	Katz et al[35]	15	15	9.8 [−6.1, 25.7]		—	.23	
According to anaesthesia maintenance									
Volatile anaesthetic	9	Agata et al,[26] Cho et al,[28] Guignard et al,[33] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Lee (2) et al,[42] Shin et al[47]	242	236	−8.1 [−28, 11.7]		100	.42	.41
Propofol	4	Florkiewicz et al,[32] Shin et al,[47] Tirault et al,[49] Zhang et al[52]	135	136	0.3 [−1.6, 2.1]		43	.78	
According to type of surgery									
Gynaecological surgery	3	Cho et al,[28] Katz et al,[35] Lee (2) et al[42]	63	64	−1.5 [−4.8, 1.8]		45	.37	.86

(Continues)

TABLE 2 (Continued)

Outcome	Number of trials	References	Total number of patients		Mean difference (95% CI)	TSA-adjusted CI	I^2 (%)	*P* value for overall effect	*P* value for subgroup differences
			Low dose	High dose					
Abdominal surgery	5	Guignard et al,[33] Kim et al,[37] Kong et al,[38] Koo et al,[39] Tirault et al[49]	129	130	−1.3 [−6.7, 4.2]		76	.65	
Cardiac surgery	1	Florkiewicz et al[32]	43	47	−0.5 [−3.7, 2.7]		–	.76	
Other surgeries	3	Agata et al,[26] Shin et al,[47] Zhang et al[52]	142	131	−13.1 [−44.4, 18.2]		100	.41	
According to post-operative analgesic regimen									
No NSAID/ Acetaminophen	12	Agata et al,[26] Cho et al,[28] Florkiewicz et al,[32] Guignard et al,[33] Katz et al,[35] Kim et al,[37] Kong et al,[38] Koo et al,[39] Lee (2) et al,[42] Shin et al,[47] Tirault et al,[49] Zhang et al[52]	377	372	−5.1 [−21.3, 11.1]		100	.54	N/A
Inclusive of NSAID/ Acetaminophen	–	–	–	–	–		–		–
Total			377	372	−5.1 [−21.3, 11.1]	Not feasible	100	.54	

Abbreviations: CI, confidence interval; N/A, not applicable; NSAID, nonsteroidal anti-inflammatory medication; TSA, trial sequential analysis.

Regarding 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 −0.17 (95% CI: −0.28, −0.06); using Trim and Fill, the imputed point estimate is −0.30 (95% CI: −0.40, −0.20), suggesting that two trials are missing. The certainty of evidence for our primary outcome was low according to the GRADE system.

Secondary acute pain-related outcomes were also significantly reduced in the low-opioid group with the exception of cumulative iv morphine equivalents consumed at 24 post-operative hours (Table 2). Six trials investigated hyperalgesia specifically and concluded that high doses of intraoperative opioids reduced the threshold for mechanical pain (mean difference to pressure [95% CI]: 3.8 g·mm^{-2} [1.8, 5.8]; TSA-adjusted CI: 0.5, 7.2; I^2 = 99%; *P* = .0003; low certainty of evidence).[34,40-42,45,51,52]

With respect to hospital-resource related outcomes, time to extubation was sought by 13 trials and was similar between groups (mean difference [95%]: 0.8 min [−0.3, 1.9]; TSA-adjusted CI: −1.3, 2.9; I^2 = 63%; *P* = .14; low certainty of evidence).[26,28,29,32-34,37,38,41,48-50,52] Only two trials reported length of stay in the post-anaesthetic care unit without identifying any difference between groups (mean difference [95%]: 1.5 min [−2.2, 5.1]; TSA-adjusted CI: −13.6, 16.5; I^2 = 47%; *P* = .44; low certainty of evidence).[40,47] No trials reported hospital length of stay or serious adverse events.

Table 3 summarises the findings according to the GRADE system.

4 | DISCUSSION

This systematic review and meta-analysis investigated whether high-dose intraoperative opioids, compared to a low-dose regimen, contributes to increased post-operative pain and hyperalgesia in the post-operative period. Based on 27 randomised controlled trials, including a total of 1630 patients under general anaesthesia, our results showed that there is overall low certainty of evidence that high-dose administration resulted in increased pain scores from 2 to 24 post-operative hours, with increased cumulative iv morphine equivalents consumed at 2 post-operative hours, and decreased mechanical pain threshold. The subgroup analysis according to intraoperative opioid regimen revealed that hyperalgesia was present with remifentanil but not with other opioids. This finding may represent a type II error as only five trials investigated opioids other than remifentanil.[27,31,35,44,51] Indeed, a post-hoc analysis revealed that a total of 740 patients would be needed to demonstrate that high-dose of non-remifentanil opioids would result in higher pain scores at 24 post-operative hours, with alpha and beta values of .05 and .2 respectively. Despite this limitation, our results provide more rigorous analysis than previous systematic reviews of opioids in general[8,11] or remifentanil specifically.[6,53] These investigations either did not conduct any statistical analysis, and based their conclusions on qualitative assessment rather than quantitative evaluation,[6,8,11] or investigated non-pain-related outcomes such as rates of awareness or post-operative nausea and vomiting.[53]

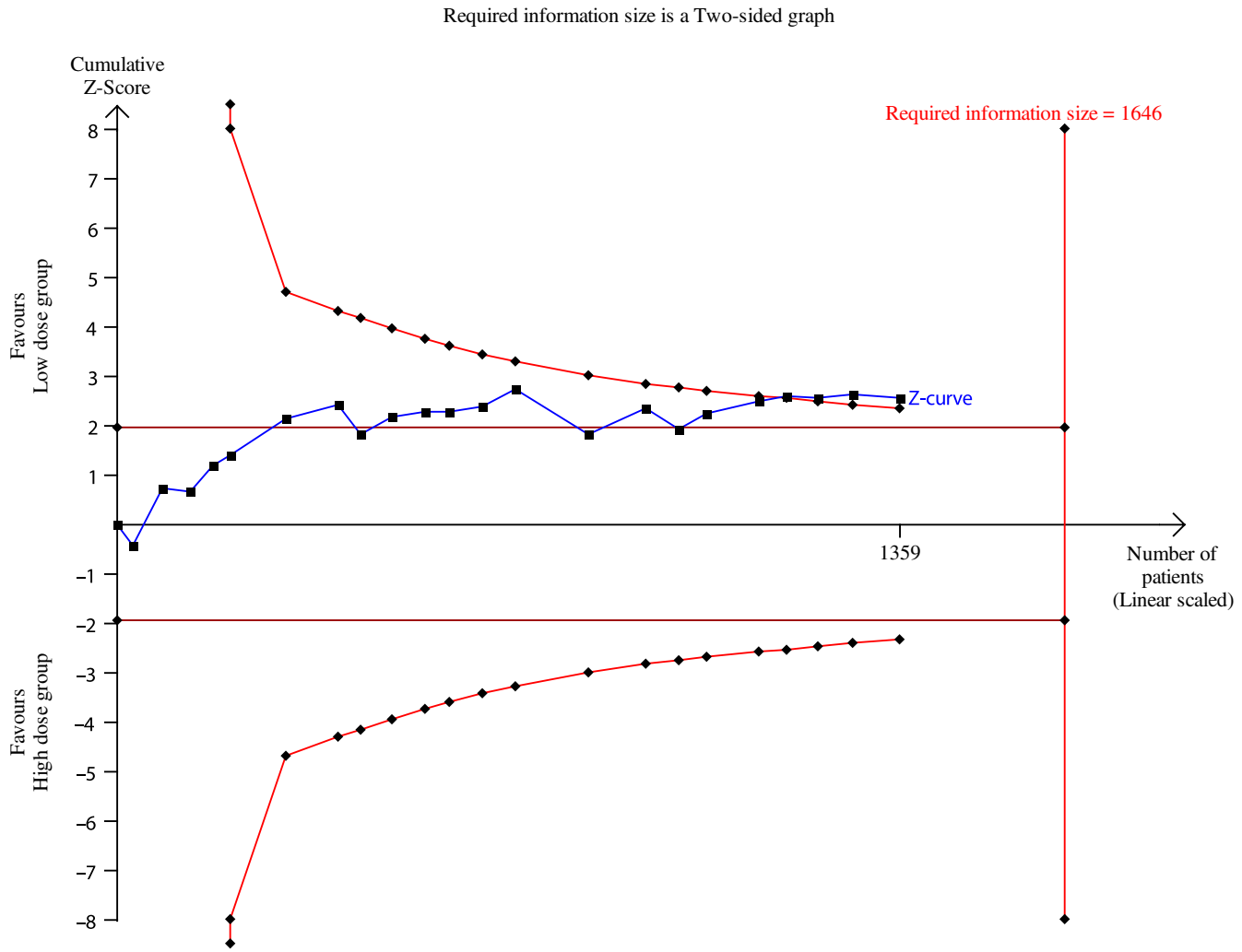

FIGURE 4 Trial sequential analysis on pain score at rest at 24 post-operative hours. The cumulative Z-curve (blue) crosses the conventional (brown) and the monitoring boundary curves (red) before reaching the required information size indicating that reliable evidence is established [Colour figure can be viewed at wileyonlinelibrary.com]

Even if statistically significant, a pain score difference of less than 0.5 and an opioid consumption difference of less than 2 mg, respectively, are clinically negligible. However, in the absence of benefit, these findings raise questions regarding the practice and justifications of administering high-dose of opioids in the intraoperative period. Given existing evidence regarding opioid contribution to immunosuppression,[54] and cancer recurrence,[55,56] as well as concerns regarding in hospital administration and association with the global opioid epidemic,[10] the results of this meta-analysis suggest that the practice of high-dose intraoperative opioid administration should be reconsidered.

In 2015, per capita opioid prescribing in the United States exceeded the amount prescribed in 1999 by fold.[57] While not a linear increase, each American now receives an average of 640 mg of morphine annually. What's more, prescribed opioids in the United Kingdom are currently responsible for more deaths than heroin.[58] In the perioperative setting, 49% of patients are discharged home with an opioid prescription after elective surgery, and up to 7% of patients who were opioid naive before surgery are still taking oral opioids 12 months after discharge.[10,59] Indeed, surgery itself has been identified as a risk factor for opioid use 1 year later, especially in men and elderly patients.[60] More precisely, there is evidence that the intensity of acute pain after surgery is strongly associated with chronic pain development in the post-operative period.[61,62] Once this path is established, opioids frequently then become the treatment of choice.[58] Given the results of this meta-analysis, the administration of general anaesthetic with low-dose intraoperative opioids is one of the two strategies that may be adopted to reduce post-operative pain, potentially impacting this trend. The other evidence-based strategy is the administration of multimodal analgesia inclusive of acetaminophen, nonsteroidal anti-inflammatories, dexamethasone, magnesium and regional anaesthetic techniques.[18,63-67]

While our analysis suggests that firm evidence has been reached for our conclusion, the following considerations should be kept in mind. The definitions of low- and high-dose opioids were not consistent and sometimes overlapped among trials. Given the nature of our research question to examine the impact of two relative doses

TABLE 3 Evidence profile

Quality assessment					Summary of findings		
Outcome	Risk of bias	Inconsistency	Indirectness	Imprecision	Total number of RCTs/participants	Conclusion/mean difference [95% CI]	Certainty of evidence (GRADE)
Pain score at rest at 2 post-operative hours (analogue scale, 0-10)	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	21/1345	Increased pain score in high dose group/−0.4 [−0.6, −0.2]	Low (⊕⊕OO)[e]
Pain score at rest 24 post-operative hours (analogue scale, 0-10)	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	21/1359	Increased pain score in high dose group/−0.2 [−0.4, −0.1]	Low (⊕⊕OO)[e]
Intravenous morphine consumption equivalents at 2 post-operative hours	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	11/647	Increased consumption in high dose group/−1.6 mg [−2.6, −0.7]	Low (⊕⊕OO)[e]
Intravenous morphine consumption equivalents at 24 post-operative hours	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	12/749	Equivalent consumption in both groups/−5.1 mg [−21.3, 11.1]	Low (⊕⊕OO)[e]
Mechanical pain threshold	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	6/361	Decreased threshold in high dose group/3.8 $g \cdot mm^{-2}$ [1.8, 5.8];	Low (⊕⊕OO)
Time to extubation	Serious[a]	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	13/668	Equivalent time to extubation in both groups/0.8 min [−0.3, 1.9]	Low (⊕⊕OO)[e]
Length of stay in post-anaesthetic care unit	Outcome reported by two studies	Serious inconsistency[b]	No serious indirectness[c]	No serious imprecision[d]	2/247	Equivalent length of stay in both groups/1.5 min [−2.2, 5.1]	Very Low (⊕OOO)[f]
Length of hospital stay	Not applicable	Not applicable	Not applicable	Not applicable	0	Inconclusive	Not applicable
Serious adverse events	Not applicable	Not applicable	Not applicable	Not applicable	0	Inconclusive	Not applicable

Note: Inconsistency, indirectness and imprecision refer to the degree of heterogeneity among trials, to the presence of a constant definition of the primary outcome, and to the clinical decision made related to the limits of the confidence interval.[20]

Abbreviation: GRADE, Grading of Recommendations, Assessment, Development and Evaluation.

[a]Only a minority of trials had an overall low risk of bias.

[b]I^2 above 50%.

[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]Certainty of evidence was initially high, as it was based on randomised controlled trials. However, as there was a concern about inconsistency, and high risk of biases, we rated the certainty of evidence down by two levels.

[f]We rated down for limitations and inconsistency, as only two trials reported this outcome.

(low versus high dose) within a given trial, we believe that this limitation does not impact the validity of our results. Furthermore, patients in the overall high dose group received at least two-thirds more opioids than the low dose group, with the exception of a single trial.[30] In addition, only one trial had an overall low risk of bias; while we contacted the authors for missing data, we did not ask for clarifications regarding the unknown risk of biases. Moreover, we cannot exclude a type-1 error but we believe that we adopted the appropriate measures to reduce this risk, such as protocol registration prior to statistical analyses, and application of a Bonferroni correction. Despite our attempt to group trials according to the type of intraoperative opioid regimen, medication used for anaesthetic maintenance, or surgery type, the coefficient of heterogeneity remained high. In addition, apart from extubating time, we were unable to draw any robust conclusions regarding the impact of general anaesthesia with high-dose intraoperative opioids on hospital resources-related outcomes. We suggest that this represents an opportune area for additional trials with consistent methodology to explore these economic outcomes. Finally, no studies reported any serious adverse event, and we recommend this outcome to be sought in the future trials, as it might impact patient health.

In conclusion, there is overall low certainty of evidence that high-dose intraoperative opioids in patients under general anaesthesia increase pain scores and contribute to hyperalgesia in the post-operative period when compared with a low-dose regimen. Our understanding of opioid management would benefit from additional robust methodology trials to better define the impact of each opioid regimen on hospital and health-system resources.

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CONFLICT OF INTEREST

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AUTHORS' CONTRIBUTIONS

EA involved in study design, literature search, statistical analysis, manuscript preparation; JF and SG involved in literature search, articles assessment and data extraction; LK involved in articles assessment and data extraction; KRK involved in articles assessment and manuscript editing;

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SUPPORTING INFORMATION

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

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