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Review Article

REVIEW ARTICLE

Efficacy of nonopioid analgesics and adjuvants in multimodal analgesia for reducing postoperative opioid consumption and complications in obesity: a systematic review and network meta-analysis

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Abstract

Background: Managing postoperative pain in patients with obesity is challenging. Although multimodal analgesia has proved effective for pain relief, the specific impacts of different nonopioid i.v. analgesics and adjuvants on these patients are not well-defined. This study aims to assess the effectiveness of nonsteroidal antiinflammatory drugs, paracetamol, ketamine, α-2 adrenergic receptor agonists, lidocaine, magnesium, and oral gabapentinoids in reducing perioperative opioid consumption and, secondarily, in mitigating the occurrence of general and postoperative pulmonary complications (POPCs), nausea, vomiting, PACU length of stay (LOS), and hospital LOS among surgical patients with obesity.
Methods: A systematic review and network meta-analysis was performed. PubMed, Scopus, Web of Science, CINAHL, and EMBASE were searched. Only English-language RCTs investigating the use of nonopioid analgesics and adjuvants in adult surgical patients with obesity were included. The quality of evidence and certainty were assessed using the RoB 2 tool and GRADE framework, respectively.
Results: In total, 37 RCTs involving 3602 patients were included in the quantitative analysis. Compared with placebo/no intervention or a comparator, dexmedetomidine, ketamine, lidocaine, magnesium, and gabapentin significantly reduced postoperative opioid consumption after surgery. Ketamine/esketamine also significantly reduced POPCs. Ibuprofen, dexmedetomidine, and lidocaine significantly reduced postoperative nausea, whereas dexmedetomidine, either alone or combined with pregabalin, and lidocaine reduced postoperative vomiting. Dexmedetomidine significantly reduced PACU LOS, whereas both paracetamol and lidocaine reduced hospital LOS.
Conclusions: Intravenous nonopioid analgesics and adjuvants are crucial in multimodal anaesthesia, reducing opioid consumption and enhancing postoperative care in adult surgical patients with obesity.
Systematic review protocol: CRD42023399373 (PROSPERO).

Keywords: anaesthesia adjuvants; analgesia; multimodal analgesia; obesity; opioid; postoperative nausea and vomiting

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Editor's key points

- Managing postoperative pain by reducing opioid use in patients with obesity is challenging.
- This systematic review and network meta-analysis shows that nonopioid i.v. analgesics and adjuvants reduce postoperative opioid consumption in patients with obesity.
- Among nonopioid i.v. analgesics and adjuvants, ketamine/esketamine reduce postoperative pulmonary complications in patients with obesity.
- Nonopioid i.v. analgesics and adjuvants, particularly dexmedetomidine, improve postoperative care in patients with obesity.

Managing postoperative pain in patients with obesity poses unique challenges.[1,2] The adoption of multimodal anaesthesia, which uses various agents to target different points of the nociceptive pathway, enhances effectiveness and minimises side effects.[3] This approach is crucial given the global increase in obesity and the resulting increase in patients with specific physiological needs requiring tailored analgesic methods.[1,2]

Multimodal anaesthesia improves pain relief in patients with obesity,[4] but its effect on reducing opioid use, which is associated with significant adverse effects and addiction risks,[1,2] is not fully understood. In the general population, opioid-induced respiratory depression can lead to hypoxaemia, hypercapnia, cardiorespiratory arrest, increased perioperative morbidity and mortality, and prolonged hospital length of stay (LOS) and costs.[5] The risk of opioid-induced respiratory depression is heightened by obesity-related physiological changes and by coexisting comorbidities, particularly cardiorespiratory diseases.[1,2,6] This risk of opioid-induced respiratory depression is significantly increased in patients with cardiac disease (odds ratio [OR] 1.79), pulmonary disease (OR 2.27), and obstructive sleep apnoea (OSA) (OR 1.4),[5] which in turn is also associated with higher rates of postoperative desaturation (OR 2.27), respiratory failure (OR 2.43), reintubation (OR 2.05), and cardiac events (OR 2.07).[1] Opioids suppress both ventilatory and pharyngeal neuromotor drive, reducing airway patency and increasing the likelihood of upper airway obstruction,[7] predisposing patients to adverse respiratory events.[1,5,6] Additionally, high-certainty evidence indicates that opioid prescribing significantly increases the risk of nausea, vomiting, constipation, dizziness, and drowsiness, without substantially reducing pain intensity after discharge.[8]

Multimodal analgesia, combining drugs, techniques, and non-pharmacological interventions, is recommended for managing postoperative pain in the general population.[9] Its effectiveness in preventing postoperative pain is particularly crucial for high-risk patients, such as those with obesity,[1,10] and is endorsed by national[6,11] and international guidelines.[12,13] In such patients, the use of nonopioid i.v. analgesics and adjuvants within a multimodal anaesthesia framework has been shown to enhance pain relief and improve overall quality of recovery after surgery.[4]

This systematic review and network meta-analysis aims to evaluate the effectiveness of multimodal analgesia in reducing opioid use and decreasing general and respiratory complications after surgery in patients with obesity, who face a higher risk of postoperative pulmonary complications (POPCs).[1,2,6,14] It also assesses the impact on PACU and hospital stay durations, critical elements in enhanced recovery protocol after surgery[11,13] for such a high-risk patient population.[1,6,12]

Methods

The protocol for this network meta-analysis was prospectively registered in the PROSPERO database on February 25, 2023, bearing the identification number CRD42023399373. Throughout the preparation of this manuscript, strict adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist was maintained.[15]

Eligibility criteria

The inclusion criteria for this systematic review and network meta-analysis were established based on the PICOS framework, detailed as follows.

Population (P)

The study targeted adult patients (aged ≥18 yr) with obesity, identified by a BMI ≥30 kg m^{-2}, who were receiving surgical treatment.

Intervention (I)

Evaluated interventions encompass a range of multimodal, nonopioid pain-relief methods as part of a conventional anaesthesiology approach. This includes the administration of nonopioid analgesics and adjuvants in multimodal general anaesthesia, covering medications such as non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol (or acetaminophen) (from here on referred to as paracetamol for convenience), ketamine, α-2 agonists (i.e. dexmedetomidine, clonidine), lidocaine, magnesium, and oral gabapentinoids (i.e. pregabalin, gabapentin).[3,4] The research will assess these treatments both as standalone options and in combination.

Comparison (C)

For comparison, the study identifies groups receiving a placebo, no treatment, or different multimodal analgesic methods, either alone or combined.

Outcomes (O)

The primary aim of this study was to assess the reduction in postoperative opioid consumption. Evaluation began from the first reported time point after surgery for the primary outcome and extended as far as was feasible, to examine potential impacts not only in the immediate postoperative period but also later on. To ensure comparability, opioids were converted to i.v. morphine milligram equivalents using the GlobalRPH morphine equivalent calculator, with a 0% cross-tolerance modifier (available at http://www.globalrph.com/narcotic).[10] Secondary endpoints included the total postoperative complications, evaluated as a composite of postoperative pulmonary complications (POPCs), as outlined in the literature,[14,16,17] and non-POPCs, all observed within the postoperative monitoring timeframe. The preselected POPCs included conditions that ranged from mild to severe respiratory failure, all characterised by hypoxaemia. This encompassed both specified criteria of desaturation—Pa_{O_2} <8 kPa (60 mm Hg), Pa_{O_2}:FI_{O_2} ratio <40 kPa (300 mm Hg), or Sp_{O_2} <90% on room air—and instances where

any degree of hypoxaemia necessitated oxygen supplementation or ventilatory support, even without a specified level of desaturation.[14,16,17] Complications also comprised acute respiratory distress syndrome, bronchospasm, new pulmonary infiltrates, infections or pneumonia, aspiration pneumonitis, pleural effusion, atelectasis, cardiopulmonary oedema, and pneumothorax, each reflecting the complexity of postoperative pulmonary management.[14,16,17] Non-POPCs were classified according to their respective categories, such as neurological (e.g. dizziness, drowsiness, headache), cardiovascular (e.g. bradycardia, tachycardia, arrhythmia, hypertension, hypotension), abdominal (e.g. constipation, paralytic ileus, abdominal distension), and other (e.g. itchiness, skin redness, drug reaction), thus providing a comprehensive overview of all potential postoperative complications. Nausea and vomiting were assessed separately within the same postoperative monitoring period. The severity of postoperative nausea and vomiting was evaluated using standardised tools, namely the Visual Analogue Scale (VAS) and the Numerical Rating Scale (NRS). Both scales are extensively used in clinical settings for their simplicity and effectiveness in evaluating pain. If pain scores were reported on a 100-point rating scale, they were converted to a 10-point rating scale for analysis. Finally, PACU and hospital length of stay (LOS) were evaluated.

Study design (S)

Eligible studies for this review are prospective randomised controlled trials (RCTs) published in the English language involving adult surgical patients with obesity. Studies excluded from this review include observational studies, non-clinical research, paediatric studies, studies lacking sufficient data or the full-text version, and non-peer-reviewed articles.

Search strategy

The search strategy was performed using the electronic databases, including PubMed, Scopus, Web of Science, CINAHL, and EMBASE, up until September 28, 2023. The search targeted specific substances including paracetamol, NSAIDs, ketamine, α-2 agonists, lidocaine, magnesium, and pregabalin/gabapentin, whether used individually or in combination.[3,4] A strategic combination of Medical Subject Headings (MeSH) and keywords was used, using Boolean operators 'AND' and 'OR' to refine the results. To ensure comprehensive coverage, reference lists of reviewed studies were also analysed to identify any studies potentially overlooked in the database search. The full search methodology, including term combinations and filters, is detailed in Supplementary material 1.

Study selection, data extraction, and data retrieval

Titles and abstracts of articles identified through the initial search strategy were independently evaluated by two authors (ET and FL) to sift out unrelated articles. Subsequently, the full texts of the filtered studies were reviewed to check their compatibility with the established inclusion criteria. Data extraction was carried out independently by the same two authors (ET and FL) utilising specially designed forms for each study. Any disagreements encountered during the selection of studies, extraction of data, or evaluation of trials were resolved by another author (MC) who had not participated in the initial literature search. Additionally, two other authors (TP and AB), who were not involved in the initial search and data extraction stages, conducted a manual review and assessment of each selected study to verify the extracted data and confirm the integrity of the final dataset. For supplementary data, corresponding authors of the included studies were approached via e-mail.

Quality assessment and certainty of evidence assessment

Quality assessment of the included RCTs was conducted independently by two authors (ET and FL) using the Risk of Bias 2 (RoB 2) tool.[18] This tool evaluates potential bias across five critical domains: the randomisation process, deviations from the planned interventions, missing outcome data, measurement of outcomes, and the selection of reported results. For each domain, a set of 'signalling questions' probes for potential bias sources. Answers to these questions feed into an algorithm that generates a risk of bias assessment for each domain, categorising it as 'low', 'high', or 'some concerns', alongside a similar overall risk of bias assessment for the study.[18] Disagreements in these initial evaluations were reconciled by consulting a third author (MC).

The Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) framework for network meta-analyses was applied to gauge the certainty of evidence, classifying it into four levels: high (⊕⊕⊕⊕), moderate (⊕⊕⊕⊖), low (⊕⊕⊖⊖), or very low (⊕⊖⊖⊖) quality of evidence (QoE).[19] At the outset, given their RCT nature, the Quality of Evidence (QoE) receives a high rating, which may be downgraded for reasons including risk of bias (e.g. inadequate blinding or allocation concealment), inconsistency (evaluated by variance in effect estimates across studies using measures of statistical heterogeneity such as tau [τ], tau-squared [τ^2], and I-squared [I^2]), indirectness (e.g. when study populations, interventions, or outcomes differ from those of primary interest), imprecision (evidenced by wide 95% confidence intervals [CIs] or estimates near a null effect), and publication bias.[19]

Tools such as network graphs, forest plots, radar plots, rankograms, and heat maps were used for data visualisation and analysis, enabling an in-depth comparison of treatment efficacy and rankings.

Statistical analysis

This network meta-analysis was performed using a frequentist approach. Between the random and fixed-effects models typically used for meta-analyses, the random-effects model was favoured in this network meta-analysis to potentially capture the variability across different studies.

Continuous outcomes were analysed by calculating the mean difference (MD) along with its 95% CI, whereas for binary outcomes, the odd ratios (OR) and 95% confidence intervals (CI) were determined. In instances where studies presented median values and interquartile ranges, they were converted to estimated mean and standard deviation using Hozo's method.[20] For both dichotomous and continuous data, effects were computed using the inverse–variance method, which has the advantage of also providing results for random effects. For dichotomous data, where studies reported no events, a correction involving the addition of 0.5 to each cell frequency was applied when calculating ORs. The analysis compared the Mantel–Haenszel method with the inverse–variance approach, revealing similar

outcomes. The DerSimonian and Laird method underpinned the inverse–variance weighting to address study heterogeneity.

Heterogeneity was assessed with the I^2 statistic, adopting a significance level of $P<0.1$ to confirm its presence, and categorising I^2 values as low (<25%), moderate (25–50%), or high (>50%).[21] To further quantify heterogeneity, τ was computed to gauge the standard deviation of effect sizes across studies, thereby measuring variability beyond mere chance. Additionally, τ^2 was calculated to estimate the variance between studies. With a limited number of studies, estimating τ^2 accurately posed a challenge yet was critical for interpreting heterogeneity. Significant heterogeneity was further corroborated by the outcomes of the Q test, which aided in the interpretation and application of the meta-analysis results. For investigating publication bias, funnel plots were examined visually, and Egger's test for asymmetry was conducted on analyses with 10 or more studies. A P-value of <0.1 in Egger's test hinted at a potential risk of publication bias, whereas a P-value of ≥0.1 indicated a negligible risk.[22] Sensitivity analyses were conducted to ensure the robustness of the findings against arbitrary or unclear decisions made during the review process. R software version 4.3.1 (2023, R Foundation for Statistical Computing, Vienna, Austria) facilitated all analyses, with the '*netmeta*' package being particularly utilised for network meta-analysis tasks. Adhering to conventional statistical norms, P-values were two-tailed, with a significance level established at <0.05.

Results

Study selection

Of the 12 088 reports initially identified for screening in the literature, 12 051 records were excluded because they did not meet the inclusion criteria. Therefore, 37 RCTs involving a total of 3602 patients were eligible for inclusion in the network meta-analysis.[23–59] No corresponding authors of the included studies were contacted. The PRISMA flow diagram of the study selection protocol is presented in Figure 1.

Study characteristics

The characteristics of the included RCTs[23–59] are available in Supplementary material 2. Out of the total participants, 1811 patients were allocated to control (1517 placebo or no intervention and 294 to comparator), and 1791 were allocated to

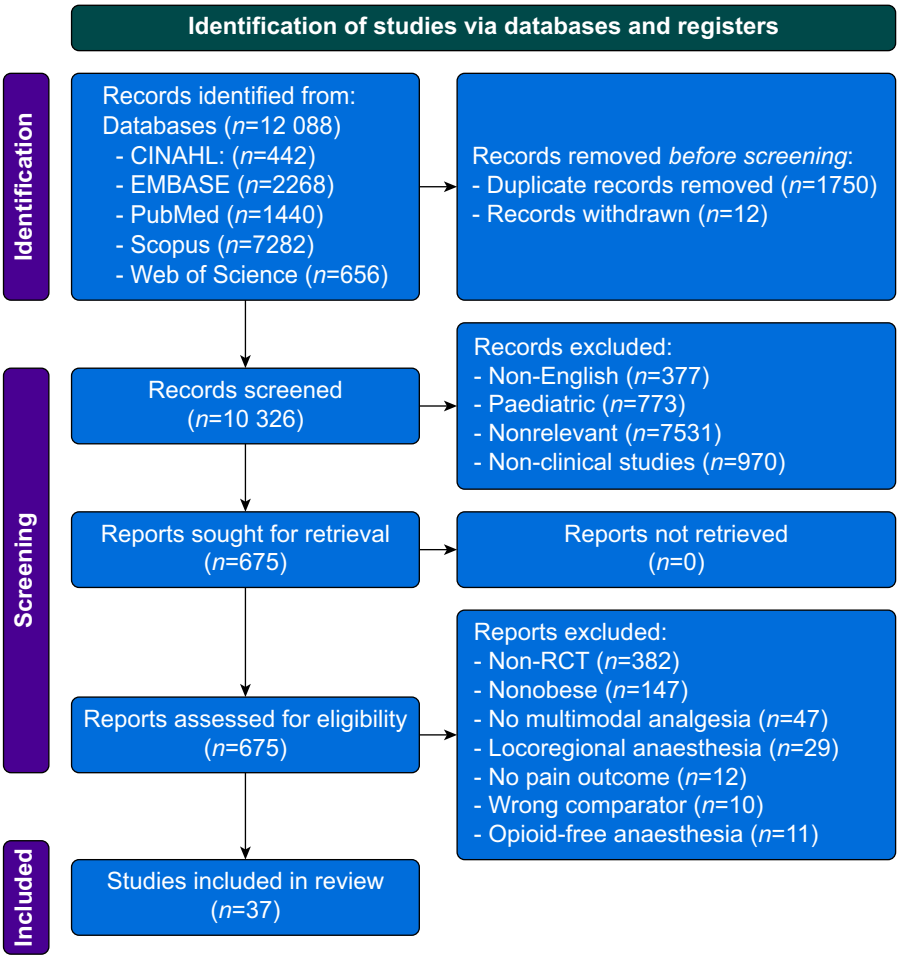

Fig 1. The PRISMA flow diagram of the study selection process.

treatment (135 to ibuprofen,[35,40] 207 to paracetamol,[32,34,36,40] 318 to ketamine,[24,26,28,45,47,48,50,51,53,57,59] 108 to ketamine plus magnesium,[47,50] 361 to dexmedetomidine,[23,25,33,38,44,55,57] 341 to lidocaine,[29,33,46,49,52,54,55,58] 110 to magnesium,[41,43,56] 112 to gabapentin,[30,39,42] 69 to pregabalin,[27,37] and 30 to pregabalin plus dexmedetomidine).[31] Regarding the comparison between treatment and comparator, paracetamol was compared with ibuprofen in 89 patients,[35,40] ketamine was compared with dexmedetomidine in 54 patients,[55,57] lidocaine in 24 patients,[55] ketamine plus magnesium in 57 patients,[47,50] and lidocaine was compared with dexmedetomidine in 70 patients.[33,55]

Risk of bias assessment

The RoB 2 assessment conducted on the included RCTs suggests that these studies demonstrate either a low or unclear risk of bias.[23–59] The distribution of risk of bias evaluations across various domains is illustrated in the weighted bar graphs presented in Figure 2. Detailed assessments of domain-level judgments for each study are available in Supplementary material 3.

Overall, all studies provided information on randomisation, but some were unclear about the randomisation process or failed to specify allocation concealment or masking strategies.[23,24,26–28,30,38,40,48,51,53,56] Moreover, certain studies did not specify the method for blinding operators and participants.[23,26,28,38,48,53,54] However, all studies reported outcome data according to the study endpoint.[23–59] Only one study declared that the outcome assessor was aware of the intervention received by the participants,[26] whereas in another study, this aspect was not clearly specified.[53]

The risk of reporting bias was deemed low across all studies,[23–59] and outcome measurements and analyses adhered to a prespecified plan to mitigate the potential for biased result selection.[23–59] Further elaboration on the reasons for the risk of bias assessments is available in Supplementary material 4.

Outcomes

Network graphs illustrating the study outcomes can be found in Supplementary material 5. However, the most representative graphs for the study endpoints are presented in the text as Figures 3 and 4. Forest plots for the network meta-analysis are accessible in Supplementary material 6, showcasing the estimated treatment effects along with their corresponding confidence intervals. Tables 1 and 2 present the results with P-scores for all outcomes, supplemented by graphical representations in Supplementary material 7, Figures S1–S8. Additionally, Supplementary material 8 contains funnel plots for the network meta-analysis, assessing the potential presence of publication bias. Rankograms from the network meta-analysis, depicting the probability distribution of treatment rankings for effectiveness across various outcomes, are available in Supplementary material 9. Finally, Supplementary material 10 presents heat maps from the separate indirect from direct evidence (SIDE) analysis, aiding in the evaluation of consistency between direct and indirect evidence within the network meta-analysis.

Postoperative opioid consumption

Opioid consumption has been evaluated at different time points after surgery, during PACU stay,[23,25,29,33,34,37,42,44,47] and at 1 h,[43,47] 2 h,[23,28,43,48] 4 h,[43,44] 8 h,[33,56] 12 h,[26,39,43] 24 h,[23,27–29,31,33,35,41–43,46,47,49–51,54,55,57,59] and 48 h[24,33,51] after surgery (Table 1). No evaluations for the specified outcomes are available beyond 48 h after surgery.

Compared with placebo/no intervention or a comparator, dexmedetomidine reduced opioid consumption during PACU stay (Mean difference MD [95% CI]: −3.9 [−4.6 to −3.3] mg, $P<0.001$, moderate Quality of Evidence (QoE)),[23,25,33,44] and at 2 h (MD [95% CI]: −5.2 [−5.7 to −4.6] mg, $P<0.001$, high QoE),[23] 8 h (MD [95% CI]: −7.8 [−8.3 to −7.3] mg, $P<0.001$, high QoE),[33] 24 h (MD [95% CI]:−5.2 [−7.4 to −2.9] mg, $P<0.001$, moderate QoE),[23,33,55,57] and 48 h (MD [95% CI]: −15 mg [−18.8 to −11.1], $P<0.001$, moderate QoE)[33] after surgery (Table 1). Dexmedetomidine combined with pregabalin reduced opioid consumption at 24 h (MD [95% CI]: −30.8 [−36.2 to −25.4] mg, $P<0.001$, moderate QoE)[31] after surgery (Table 1).

Compared with placebo/no intervention or a comparator, lidocaine significantly reduced opioid consumption during PACU stay (MD [95% CI]: −3.2 [−4.1 to −2.4] mg, $P<0.001$, moderate QoE),[29,33] and at 8 h (MD [95% CI]: −6.3 [−6.8 to −5.7] mg, $P<0.001$, high QoE),[33] 24 h (MD [95% CI]: −6.4 [−8.7 to −4.1] mg, $P<0.001$, moderate QoE),[29,33,46,49,54,55] and 48 h (MD [95% CI]: −11 [−14.8 to −7.1] mg, $P<0.001$, moderate QoE)[33] after surgery (Table 1).

Compared with placebo/no intervention or a comparator, ketamine significantly reduced opioid consumption during PACU stay (MD [95% CI]: −2 [−4.0 to −0.07] mg, $P=0.042$,

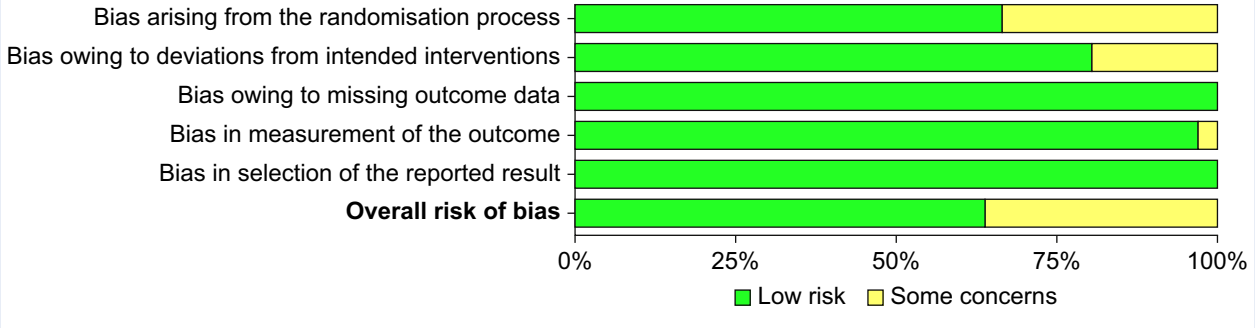

Fig 2. Summary plot of RoB 2 assessment for the included RCTs.

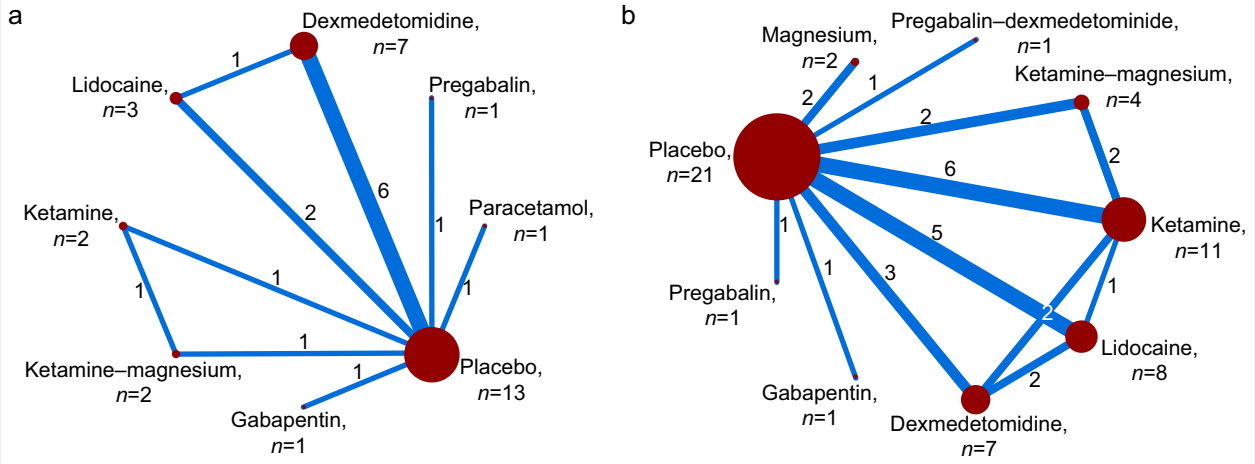

Fig 3. Network graphs corresponding to postoperative opioid consumption during the PACU stay (a) and at 24 h after surgery (b). In these graphs, node size (red circles) is proportional to the number of trials evaluating that intervention, and the blue lines represent the number of comparisons between each treatment.

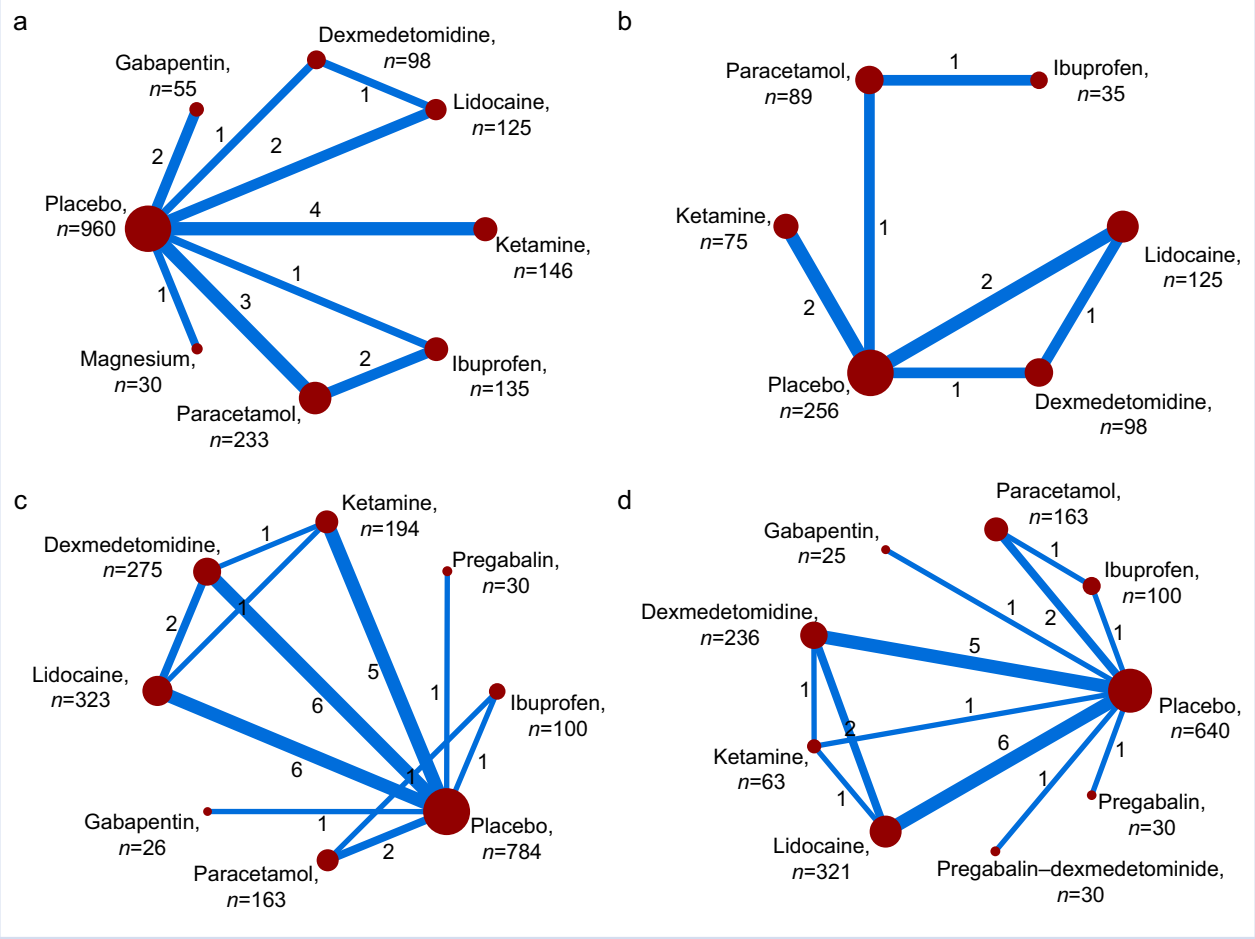

Fig 4. Network graphs reporting treatment effect for total postoperative complications (a), postoperative pulmonary complications (POPCs) (b), nausea (c), and vomiting (d). In these graphs, node size (red circles) is proportional to the number of trials evaluating that intervention, and the blue lines represent the number of comparisons between each treatment.

Table 1 Effects of i.v. nonopioid agents and adjuvants on opioid consumption. 95% CI, 95% confidence interval (mg); MD, mean difference (mg); QoE, quality of evidence. P-score: The P-score reflects the effectiveness of the treatment, with higher values indicating greater effectiveness. It provides an effectiveness-based order of treatments. τ^2: Between-study variance in random-effects meta-analysis. τ: Standard deviation estimate of effect sizes in random-effects meta-analysis. I^2: Measures percentage variation across studies owing to heterogeneity; Q test: Cochran's Q test assesses heterogeneity among study results. *Downgraded one level for inconsistency (such as heterogeneity of estimates of effects across trials).[19] ‡Because of the unavailability of key heterogeneity metrics (τ^2, τ, I^2), all reported as NA, it was not possible to assess variability between studies. Consequently, this uncertainty has to downgrading one level of QoE for the outcome.[19] ¶Downgraded one level for imprecision (e.g. 95% CIs are wide and include or are close to null effect).[19] High QoE (⊕⊕⊕⊕): The authors are very confident that the true effect lies close to that of the estimate of the effect. Moderate QoE (⊕⊕⊕⊖): The authors are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low QoE (⊕⊕⊖⊖): The authors' confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.[19]

PACU stay	**τ^2=0.2854; τ=0.5342; I^2=65.7% (30.3%–83.1%); P=0.003 at Q test**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	**−3.9**	**(−4.6 to −3.3)**	**<0.001**	**0.946**	⊕⊕⊕⊖ Moderate*
Lidocaine	**−3.2**	**(−4.1 to −2.4)**	**<0.001**	**0.742**	⊕⊕⊕⊖ Moderate*
Gabapentin	**−2.6**	**(−3.9 to −1.3)**	**<0.001**	**0.573**	⊕⊕⊕⊖ Moderate*
Ketamine–magnesium	**−2.4**	**(−4.4 to −0.4)**	**0.014**	**0.547**	⊕⊕⊕⊖ Moderate*
Paracetamol	−2.0	(−6.2 to 2.2)	0.351	0.466	⊕⊕⊖⊖ Low*,¶
Ketamine	**−2.0**	**(−4.0 to −0.07)**	**0.042**	**0.437**	⊕⊕⊕⊖ Moderate*
Pregabalin	−0.9	(−3.0 to 1.2)	0.410	0.228	⊕⊕⊖⊖ Low*,¶
Placebo	–	–	–	*0.058*	
1 h after surgery	**τ^2=0; τ=0; I^2=0%; P=1.0 at Q test**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Magnesium	**−3.1**	**(−4.3 to −1.9)**	**<0.001**	**0.995**	⊕⊕⊕⊕ High
Ketamine–magnesium	**−1.2**	**(−2.3 to −0.1)**	**0.023**	**0.559**	⊕⊕⊕⊕ High
Ketamine	−1.0	(−2.0 to 0.07)	0.067	0.430	⊕⊕⊕⊖ Moderate¶
Placebo	–	–	–	*0.015*	
2 h after surgery	**τ^2=0; τ=0; I^2=0%; P=0.379 at Q test**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	**−5.2**	**(−5.7 to −4.6)**	**<0.001**	**0.999**	⊕⊕⊕⊕ High
Ketamine	**−2.5**	**(−4.1 to −0.9)**	**0.002**	**0.574**	⊕⊕⊕⊕ High
Magnesium	**−1.9**	**(−3.0 to −0.8)**	**<0.001**	**0.425**	⊕⊕⊕⊕ High
Placebo	–	–	–	*0.000*	
4 h after surgery	**τ^2=NA; τ=NA; I^2=NA**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	−6.9	(−15.4 to 1.5)	0.108	0.908	⊕⊕⊖⊖ Low‡,¶
Magnesium	**−1.9**	**(−3.1 to −0.7)**	**0.001**	**0.563**	⊕⊕⊕⊖ Moderate‡
Placebo	–	–	–	*0.027*	
8 h after surgery	**τ^2=0; τ=0; I^2=0%; P=1.0 at Q test**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Magnesium	**−9.5**	**(−12.2 to −6.8)**	**<0.001**	**0.958**	⊕⊕⊕⊕ High
Dexmedetomidine	**−7.8**	**(−8.3 to −7.3)**	**<0.001**	**0.704**	⊕⊕⊕⊕ High
Lidocaine	**−6.3**	**(−6.8 to −5.7)**	**<0.001**	**0.336**	⊕⊕⊕⊕ High
Placebo	–	–	–	*0.000*	
12 h after surgery	**τ^2=NA; τ=NA; I^2=NA**				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Gabapentin	**−5.2**	**(−9.1 to −1.3)**	**0.007**	**0.827**	⊕⊕⊕⊖ Moderate‡
Magnesium	**−3.8**	**(−5.6 to −2.1)**	**<0.001**	**0.597**	⊕⊕⊕⊖ Moderate‡
Ketamine–clonidine	**−3.8**	**(−5.0 to −2.5)**	**<0.001**	**0.574**	⊕⊕⊕⊖ Moderate‡
Placebo	–	–	–	*0.001*	

Continued

Table 1 Continued

24 h after surgery	τ^2=6.5841; τ=2.5659; I^2=86.7% (81% to 90.7%); P<0.001 at Q test				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Pregabalin–dexmedetomidine	**−30.8**	**(−36.2 to −25.4)**	**<0.001**	**1.000**	⊕⊕⊕⊖ Moderate*
Gabapentin	**−12.7**	**(−18.1 to −7.2)**	**<0.001**	**0.822**	⊕⊕⊕⊖ Moderate*
Pregabalin	**−11.5**	**(−17.8 to −5.2)**	**<0.001**	**0.782**	⊕⊕⊕⊖ Moderate*
Lidocaine	**−6.4**	**(−8.7 to −4.1)**	**<0.001**	**0.593**	⊕⊕⊕⊖ Moderate*
Dexmedetomidine	**−5.2**	**(−7.4 to −2.9)**	**<0.001**	**0.480**	⊕⊕⊕⊖ Moderate*
Magnesium	−3.4	(−7.1 to 0.3)	0.075	0.324	⊕⊕⊖⊖ Low*,¶
Ketamine–magnesium	−2.5	(−7.2 to 2.1)	0.284	0.254	⊕⊕⊖⊖ Low*,¶
Ketamine	**−2.2**	**(−4.3 to −0.1)**	**0.038**	**0.217**	⊕⊕⊕⊖ Moderate*
Placebo	–	–	–	*0.024*	
48 h after surgery	τ^2=4.8553; τ=2.2035; I^2=77.1% (25.5% to 93%); P=0.012 at Q test				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	**−15.0**	**(−18.8 to −11.1)**	**<0.001**	**0.851**	⊕⊕⊕⊖ Moderate*
Ketamine	**−14.4**	**(−19.0 to −9.8)**	**<0.001**	**0.765**	⊕⊕⊕⊖ Moderate*
Lidocaine	**−11.0**	**(−14.8 to −7.1)**	**<0.001**	**0.382**	⊕⊕⊕⊖ Moderate*
Placebo	–	–	–	*0.000*	

moderate QoE),[47] and at 2 h (MD [95% CI]: −2.5 [−4.1 to −0.9] mg, P=0.002, high QoE),[28,48] 24 h (MD [95% CI]: −2.2 [−4.3 to −0.1] mg, P=0.038, moderate QoE),[28,47,50,51,57,59] and 48 h (MD [95% CI]: −14.4 [−19 to −9.8] mg, P<0.001, moderate QoE)[24,51] after surgery (Table 1). A *post hoc* sensitivity analysis excluding the esketamine study[59] confirmed the benefit of ketamine[24,26,28,45,47,48,50,51,53,57] in reducing opioid consumption at 24 h (Supplementary material 11). Ketamine combined with magnesium reduced opioid consumption during PACU stay (MD [95% CI]: −2.4 [−4.4 to −0.4] mg, P=0.014, moderate QoE)[47] and at 1 h (MD [95% CI]: −1.2 [−2.3 to −0.1] mg, P=0.023, high QoE)[47] after surgery (Table 1).

Compared with placebo/no intervention or a comparator, magnesium significantly reduced opioid consumption at 1 h (MD [95% CI]: − 3.1 [−4.3 to −1.9] mg, P<0.001, high QoE),[43] 2 h (MD [95% CI]: −1.9 [−3 to −0.8] mg, P<0.001, high QoE),[43] 4 h (MD [95% CI]: −1.9 [−3.1 to −0.7] mg, P=0.001, moderate QoE),[43] and 8 h (MD [95% CI]: −9.5 [−12.2 to −6.8] mg, P<0.001, high QoE)[56] after surgery (Table 1).

Compared with placebo/no intervention or a comparator, gabapentin significantly reduced opioid consumption during PACU stay (MD [95% CI]: −2.6 [−3.9 to −1.3] mg, P<0.001, moderate QoE)[42] and at 24 h (MD [95% CI]: −12.7 [−18.1 to −7.2] mg, P<0.001, moderate QoE)[42] after surgery (Table 1). Pregabalin significantly reduced opioid consumption at 24 h (MD [95% CI]: −11.5 [−17.8 to −5.2] mg, P<0.001, moderate QoE)[27] after surgery (Table 1).

Compared with placebo/no intervention or a comparator, no other drugs alone or in combination were shown to reduce opioid consumption in the postoperative period.

Ibuprofen, compared with paracetamol, did not show a significant reduction in opioid consumption at 24 h (MD [95% CI]: −6.2 [−12.5 to 0.1] mg, P=0.0508) after surgery.[35]

The P-scores are detailed in Table 1 and seen as a graph in Supplementary material 7, Figure S1.

Table 1 details the QoE assessments. At PACU stay, 88% of studies contributed to a moderate QoE and 12% to a low QoE. At 1 h, 60% of studies contributed to a high QoE and 40% to a moderate QoE. At 2 h, all studies (100%) contributed to a high QoE. At 4 h, the contribution was evenly split with 50% to moderate and 50% to low QoE. At 8 h, all studies contributed to a high QoE. At 12 h, 100% of studies contributed to a moderate QoE. At 24 h, 83% of studies contributed to a moderate QoE and 17% to a low QoE. At 48 h, all studies contributed to a moderate QoE.

Postoperative complications

The impact of nonopioid analgesics and adjuvants on postoperative complications was assessed in 25 studies.[23–25,27,30,32,33,35–40,42,45,47,48,50,51,53–57,59]

Among postoperative pulmonary complications (POPCs), respiratory failure was observed in 95.2% of cases reported,[24,33,35,54,59] atelectasis in 1.6%,[35] pleural effusion in 1.6%,[35] and pneumonia in 1.6%.[32] Within the cases of respiratory failure, 40.3% required oxygen therapy,[59] and 16.1% needed ventilatory support.[33,35]

Among non-POPCs, neurological complications were noted in 63.7% of cases reported,[24,30,35,42,45,54,56] cardiovascular complications in 3%,[56] abdominal complications in 16.3%,[24,32,35,51,54] and other complications in 17%.[24,35,36,40]

Compared with placebo/no intervention or a comparator, ketamine was shown to impact postoperative complications, specifically reducing the likelihood of POPCs (OR [95% CI]: 0.37 [0.17 to 0.80], P=0.011, moderate QoE)[24,45,48,50,51,53,57,59] (Table 2). No other drugs, whether alone or in combination, demonstrated a reduction in either POPCs or non-POPCs (Table 2). A *post hoc* sensitivity analysis excluding the esketamine study[59] did not confirm the benefit of ketamine[24,26,28,45,47,48,50,51,53,57] in reducing the likelihood of POPCs (Supplementary material 11).

The P-scores are detailed in Table 2 and seen as graphs in Supplementary material 7, Figures S2–S4.

The QoE for the measured outcomes is detailed in Table 2. All studies (100%) contributed to achieving a high QoE regarding total postoperative complications, POPCs and non-POPCs.

Postoperative nausea

Postoperative nausea was evaluated in 19 studies.[23–25,28,29,33,34,37,38,40,42,45,46,48,49,53–55,58] Ibuprofen (OR [95% CI]: 0.09 [0.01 to 0.55], P=0.009, moderate QoE),[40]

dexmedetomidine (OR [95% CI]: 0.39 [0.21 to 0.72], P=0.002, moderate QoE),[23,25,33,38,55] and lidocaine (OR [95% CI]: 0.48 [0.27 to 0.84], P=0.010, moderate QoE)[29,33,46,49,54,55,58] resulted in a reduction in the incidence of postoperative nausea when compared with placebo/no intervention or a comparator (Table 2).

The P-scores are detailed in Table 2 and seen as a graph in Supplementary material 7, Figure S5.

The QoE for the measured outcomes is detailed in Table 2. Regarding nausea, 55.5% of studies contributed to a moderate QoE and 44.5% to a low QoE.

Table 2 Effects of i.v. nonopioid agents and adjuvants on postoperative complications and length of stay. 95% CI, 95% confidence interval; LOS, length of stay; MD, mean difference; OR, odds ratio; POPCs, postoperative pulmonary complications; QoE, quality of evidence. P-score: The P-score reflects the effectiveness of the treatment, with higher values indicating greater effectiveness. It provides an effectiveness-based order of treatments. τ^2: Between-study variance in random-effects meta-analysis. τ: Standard deviation estimate of effect sizes in random-effects meta-analysis. I^2: Measures percentage variation across studies owing to heterogeneity. Q test: Cochran's Q test assesses heterogeneity among study results. *Downgraded one level for inconsistency (such as heterogeneity of estimates of effects across trials).[19] †Although a low I^2 value usually suggests low heterogeneity, the quality of evidence for this observation remains uncertain. This uncertainty arises from a broad I^2 CI, which hints at potential undetected heterogeneity. Despite the reported absence of between-study variance (τ^2=0) and no variation in effect estimates (τ=0), and an I^2 of 0%, the QoE for the outcome was prudently downgraded one level.[19] ‡Because of the unavailability of key heterogeneity metrics (τ^2, τ, I^2), all reported as NA, it was not possible to assess variability between studies. Consequently, this uncertainty led to downgrading one level of QoE for the outcome.[19] ¶Downgraded one level for imprecision (e.g. 95% CIs are wide and include or are close to null effect).[19] Moderate QoE (⊕⊕⊕⊖): The authors are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low QoE (⊕⊕⊖⊖): The authors' confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.[19]

Total postoperative complications		τ^2=1.0295; τ=1.0146; I^2=61.4% (25.6% to 80%); P=0.003 at Q test			
Drug	OR	95% CI	P-value	P-score	QoE
Dexmedetomidine	0.25	(0.02–2.45)	0.235	0.775	⊕⊕⊖⊖ Low*,¶
Ibuprofen	0.32	(0.05–2.07)	0.235	0.741	⊕⊕⊖⊖ Low*,¶
Gabapentin	0.34	(0.06–1.88)	0.216	0.723	⊕⊕⊖⊖ Low*,¶
Lidocaine	0.78	(0.16–3.84)	0.764	0.452	⊕⊕⊖⊖ Low*,¶
Paracetamol	0.79	(0.18–3.44)	0.757	0.439	⊕⊕⊖⊖ Low*,¶
Ketamine	0.89	(0.24–3.25)	0.870	0.405	⊕⊕⊖⊖ Low*,¶
Placebo	–	–	–	0.339	–
Magnesium	4.46	(0.22–90.16)	0.329	0.122	⊕⊕⊖⊖ Low*,¶
POPCs		**τ^2=0; τ=0; I^2=0% (0.0% to 84.7%); P=0.727 at Q test**			
Drug	**OR**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	0.23	(0.04–1.30)	0.097	0.735	⊕⊕⊖⊖ Low†,¶
Ketamine	**0.37**	**(0.17 to 0.80)**	**0.011**	**0.620**	⊕⊕⊕⊖ Moderate†
Paracetamol	0.32	(0.01–8.21)	0.496	0.587	⊕⊕⊖⊖ Low†,¶
Ibuprofen	0.36	(0.00–16.41)	0.604	0.541	⊕⊕⊖⊖ Low†,¶
Lidocaine	0.71	(0.24–2.13)	0.554	0.338	⊕⊕⊖⊖ Low†,¶
Placebo	–	–	–	0.176	–
Non-POPCs		**τ^2=1.2379; τ=1.1126; I^2=61.1% (19.3% to 81.2%); P=0.008 at Q test**			
Drug	**OR**	**95% CI**	**P-value**	**P-score**	**QoE**
Ibuprofen	0.33	(0.04–2.36)	0.270	0.814	⊕⊕⊖⊖ Low*,¶
Gabapentin	0.34	(0.05–2.11)	0.248	0.798	⊕⊕⊖⊖ Low*,¶
Paracetamol	0.88	(0.17–4.38)	0.878	0.510	⊕⊕⊖⊖ Low*,¶
Placebo	–	–	–	0.481	–
Lidocaine	1.50	(0.12–18.76)	0.749	0.384	⊕⊕⊖⊖ Low*,¶
Ketamine	1.59	(0.37–6.71)	0.523	0.326	⊕⊕⊖⊖ Low*,¶
Magnesium	4.46	(0.19–102.71)	0.350	0.184	⊕⊕⊖⊖ Low*,¶
Postoperative nausea		**τ^2=0.3521; τ=0.5934; I^2=48.2% (14% to 68.8%); P=0.007 at Q test**			
Drug	**OR**	**95% CI**	**P-value**	**P-score**	**QoE**
Ibuprofen	**0.09**	**(0.01 to 0.55)**	**0.009**	**0.970**	⊕⊕⊕⊖ Moderate*
Dexmedetomidine	**0.39**	**(0.21 to 0.72)**	**0.002**	**0.751**	⊕⊕⊕⊖ Moderate*
Lidocaine	**0.48**	**(0.27 to 0.84)**	**0.010**	**0.663**	⊕⊕⊕⊖ Moderate*
Gabapentin	0.60	(0.09–3.74)	0.587	0.543	⊕⊕⊖⊖ Low*,¶
Paracetamol	0.71	(0.26–1.93)	0.510	0.486	⊕⊕⊖⊖ Low*,¶
Placebo	–	–	–	0.332	–
Ketamine	1.59	(0.74–3.41)	0.230	0.158	⊕⊕⊖⊖ Low*,¶
Pregabalin	2.66	(0.51–13.73)	0.240	0.094	⊕⊕⊖⊖ Low*,¶

Continued

Table 2 Continued

Postoperative vomiting	τ^2=0; τ=0; I^2=0% (0.0% to 52.3%); P=0.601 at Q test				
Drug	**OR**	**95% CI**	**P-value**	**P-score**	**QoE**
Pregabalin–dexmedetomidine	**0.06**	**(0.00 to 0.58)**	**0.014**	**0.945**	⊕⊕⊕⊖ Moderate†
Dexmedetomidine	**0.26**	**(0.13 to 0.51)**	**<0.001**	**0.787**	⊕⊕⊕⊖ Moderate†
Lidocaine	**0.32**	**(0.19 to 0.55)**	**<0.001**	**0.703**	⊕⊕⊕⊖ Moderate†
Gabapentin	0.30	(0.02–3.15)	0.319	0.686	⊕⊕⊖⊖ Low†,¶
Ibuprofen	0.58	(0.19–1.76)	0.344	0.542	⊕⊕⊖⊖ Low†,¶
Placebo	–	–	–	0.382	–
Paracetamol	1.53	(0.71–3.27)	0.296	0.240	⊕⊕⊖⊖ Low†,¶
Pregabalin	2.25	(0.50–9.99)	0.286	0.183	⊕⊕⊖⊖ Low†,¶
Ketamine	**5.48**	**(1.77 to 16.89)**	**0.003**	**0.028**	⊕⊕⊕⊖ Moderate†
PACU LOS (min)	τ^2=0; τ=0; I^2=0% (0.0% to 79.2%); P=0.628 at Q test				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Dexmedetomidine	**−20.8**	**(−31.5 to −10.2)**	**<0.001**	**0.977**	⊕⊕⊕⊖ Moderate†
Pregabalin	−6.0	(−24.7 to 12.7)	0.529	0.556	⊕⊕⊖⊖ Low†,¶
Gabapentin	−1.4	(−10.7 to 7.9)	0.770	0.392	⊕⊕⊖⊖ Low†,¶
Placebo	–	–	–	0.295	–
Lidocaine	0.05	(−1.2 to 1.3)	0.938	0.278	⊕⊕⊖⊖ Low†,¶
Hospital LOS (days)	τ^2=0.0035; τ=0.0594; I^2=8.8% (0.0% to 46.9%); P=0.357 at Q test				
Drug	**MD**	**95% CI**	**P-value**	**P-score**	**QoE**
Paracetamol	**−0.2**	**(−0.4 to −0.02)**	**0.032**	**0.837**	⊕⊕⊕⊖ Moderate*
Lidocaine	**−0.1**	**(−0.3 to −0.04)**	**0.011**	**0.756**	⊕⊕⊕⊖ Moderate*
Ibuprofen	−0.1	(−6.4 to 6.1)	0.969	0.510	⊕⊕⊖⊖ Low*,¶
Placebo	–	–	–	0.441	–
Ketamine	0.06	(−0.1 to 0.2)	0.435	0.306	⊕⊕⊖⊖ Low*,¶
Dexmedetomidine	0.1	(−0.07 to 0.4)	0.165	0.147	⊕⊕⊖⊖ Low*,¶

Postoperative vomiting

Postoperative vomiting was evaluated in 17 studies.[23,25,28,29,31,33,34,37,38,40,42,46,48,49,54,55,58] Dexmedetomidine, alone (OR [95% CI]: 0.26 [0.13 to 0.51], P<0.001, moderate QoE)[23,25,33,38,55] or combined with pregabalin (OR [95% CI]: 0.06 [0.00 to 0.58], P=0.014, moderate QoE),[31] and lidocaine (OR [95% CI]: 0.32 [0.19 to 0.55], P<0.001, moderate QoE)[29,33,46,49,54,55,58] resulted in a reduction in the incidence of postoperative vomiting compared with placebo/no intervention or a comparator. Ketamine (OR [95% CI]: 5.48 [1.77 to 16.89], P=0.003, moderate QoE)[28,48,55] resulted in an increase in the incidence of postoperative vomiting compared with placebo/no intervention or a comparator (Table 2).

The P-scores are detailed in Table 2 and seen as a graph in Supplementary material 7, Figure S6.

The QoE for the measured outcomes is detailed in Table 2. Regarding vomiting, 74% of studies contributed to a moderate QoE and 26% to a low QoE.

PACU and hospital length of stay (LOS)

The PACU LOS was evaluated in six studies.[25,37,42,44,52,54] Compared with placebo/no intervention or a comparator, only dexmedetomidine (MD [CI]: −20.8 [−31.5 to −10.2] min, P<0.001, moderate QoE)[25,44] decreased PACU LOS (Table 2).

The hospital LOS was evaluated in 14 studies.[25,29,34–37,45,49,51–55,59] Compared with placebo/no intervention or a comparator, both paracetamol (MD [95% CI]: −0.2 [−0.4 to −0.02] days, P=0.032, moderate QoE)[34–36] and lidocaine (MD [95% CI]: −0.1 [−0.3 to −0.04] days, P=0.011, moderate QoE)[29,49,52,54,55] decreased the LOS (Table 2). These results were confirmed in a *post hoc* sensitivity analysis excluding the esketamine study[59] from the ketamine studies[24,26,28,45,47,48,50,51,53,57] (Supplementary material 11).

The P-scores are detailed in Table 2 and seen as graphs in Supplementary material 7, Figures S7 and S8.

The QoE for the measured outcomes is detailed in Table 2. Regarding PACU LOS, 50% of studies contributed to moderate QoE and 50% to low QoE. Regarding hospital LOS, 75% of studies contributed to moderate QoE and 25% to low QoE.

Discussion

Our systematic review and network meta-analysis demonstrates that i.v. nonopioid analgesics and adjuvants, when utilised within a multimodal anaesthesia framework, markedly decrease opioid use and minimise side effects and complications after surgery in adult patients with obesity. Dexmedetomidine, especially when combined with pregabalin, and also ketamine, lidocaine, magnesium, and oral gabapentinoids significantly reduced postoperative opioid use up to 48 h after surgery. Ketamine/esketamine effectively reduced the risk of postoperative pulmonary complications (POPCs). Additionally, ibuprofen, dexmedetomidine, and lidocaine substantially lowered the incidence of postoperative nausea and vomiting. Dexmedetomidine decreased the duration of PACU length of stay (LOS), whereas both paracetamol and lidocaine reduced the overall hospital LOS.

Several meta-analyses have demonstrated the effectiveness of NSAIDs,[60] paracetamol,[61] ketamine,[62] dexmedetomidine,[63,64] clonidine,[65] lidocaine,[66] and magnesium,[67,68] in providing pain relief compared with control, although the

efficacy of magnesium in patients with obesity remains unclear, as it was not statistically significant in a meta-analysis of few RCTs (P=0.0905).[69] Preoperative oral gabapentinoids have also shown effectiveness.[70] When administered as part of a multimodal analgesia approach, these medications enhance pain relief and improve recovery quality in patients with obesity undergoing surgery.[4] However, effective pain relief does not automatically lead to a reduction in opioid consumption.[9] Individually, only paracetamol,[61] ketamine,[56] dexmedetomidine,[63,64] and lidocaine[66] have been noted to reduce opioid consumption in patients with obesity. Clonidine has been reported to impact overall analgesic consumption.[65] Although the reduction of opioid consumption by NSAIDs[71] and magnesium[67,68] is well-documented in the general patient population, this study uniquely highlights the benefits of magnesium in patients with obesity, but lacks specific data to confirm a significant impact of NSAIDs on opioid consumption in this subgroup of patients.

Opioids modulate pain primarily by binding to receptors in the brain and spinal cord, reducing pain perception and emotional response.[3] Nonopioid analgesics and adjuvants, however, act on various targets within the nociceptive system to decrease pain and opioid reliance.[3,72] These combined actions effectively reduce overall pain and postoperative opioid requirements.[3,72] Differences in reducing opioid consumption among nonopioid analgesics and adjuvants may also be attributed to variations in the duration of effect, largely dependent on the pharmacokinetic properties and mechanisms within the nociceptive system for controlling postoperative pain. Dexmedetomidine, with a half-life of 2–3 h,[63,64] and clonidine, with a half-life of 8–12 h,[65] may show different timing effects on pain relief.[4] However, dexmedetomidine's neuroprotective properties could extend its analgesic effects beyond the early postoperative period,[73] benefiting patients with chronic pain unresponsive to opioids.[74] Ketamine significantly impacts pain relief within the first 12 h after surgery[62,75] and offers modest benefits thereafter,[4] even if, in adult surgical patients, the use of ketamine/esketamine in the perioperative period is associated with improved early subjective quality of recovery, reduced pain severity, and fewer psychological symptoms without an increased likelihood of adverse events.[59,62] Because of the lack of recent trials directly comparing i.v. racemic ketamine and esketamine in clinical anaesthesia and analgesia, the evidence for the superior antinociceptive efficacy of either drug remains inconsistent.[76] However, ketamine also provides dose-dependent antidepressant effects that appear within hours and last 4–7 days.[77,78] Any form of ketamine is effective and safe for treating depression, showing improved response and remission and reduced depression severity compared with placebo.[79] Racemic ketamine, however, appears to be more efficacious than esketamine.[80] In a general patient population, ketamine effectively reduces anxiety and depression within 3 days after surgery, alleviating negative mood states and enhancing pain tolerance.[81] In patients with obesity, these agents significantly improve the comprehensive evaluation of pain, particularly the affective component of pain, during the postoperative period.[4,45] Lidocaine infusion not only benefits acute nociceptive pain, but also demonstrates potential in treating neuropathic conditions, providing long-term relief for patients with chronic pain,[82] and benefiting patients with obesity with both acute and chronic inflammatory pain.[4] The positive analgesic effects of systemic magnesium in diminishing postoperative pain among general surgical patients[67,68] and in patients with obesity[4] may justify its effect on opioid consumption within 8-h postoperative period. Oral gabapentinoids significantly reduce pain scores within the first 4 h after surgery, extending the benefit over the subsequent 4 h,[70] a trend also observed in patients with obesity.[4] This effect likely diminishes as time progresses owing to peak plasma concentrations occurring 1–3 h after intake and an elimination half-life of 5–9 h.[83] However, other mechanisms not directly related to neurotransmitter release at the dorsal horn, such as inhibition of descending serotonergic facilitation, stimulation of descending inhibition, anti-inflammatory actions, and influence on the affective component of pain, may explain the observed reduction in opioid consumption on the first postoperative day.[72]

Opioids suppress respiration by acting on the brainstem and carotid bodies, reducing the ventilatory response to hypoxaemia and hypercapnia and increasing the risk of respiratory complications after surgery.[84] This risk is particularly high in patients with pulmonary or cardiac conditions (increased risks of 2.27-fold and 1.79-fold, respectively) and obesity.[5] In patients with OSA, opioids reduce arousal responses essential for airway maintenance, substantially increasing the likelihood of respiratory depression and adverse respiratory events.[5,84] General anaesthesia compounds these risks by promoting upper airway obstruction.[7] However, ketamine, particularly in low doses, minimally affects central respiratory drive and may improve airway collapsibility and ventilatory carbon dioxide sensitivity, thus potentially reducing opioid-induced respiratory depression.[85]

In the general patient population, opioid-free analgesia significantly reduces the risk of non-POPCs, such as nausea and vomiting,[8] which are particularly prevalent in patients affected by obesity, with an estimated incidence of 21%.[60] Additionally, opioid-free analgesia can help to significantly mitigate symptoms such as constipation, dizziness, and drowsiness.[8] Postoperative pain (OR 2.20) and opioid consumption (OR 2.22) are significant risk factors for postoperative nausea and vomiting in patients with obesity.[86] Thus, it is reasonable that NSAIDs, lidocaine, and α-2 agonists, alone or in combination with oral gabapentinoids, reduce the incidence risk of nausea and vomiting through their analgesic and sedative properties.[4,60,63–65] In the general population of patients, dexmedetomidine significantly reduces the risk of postoperative nausea and vomiting compared with placebo (OR 0.56),[87] with consistent benefits observed also in patients with obesity[88] and confirmed by meta-regression across varying levels of perioperative care.[89] Lidocaine reduces nausea (but not vomiting) (relative risk 0.78) when administered in the first 72 h after surgery.[90] Although ketamine improves recovery quality in the general population,[81] it does not decrease the incidence of postoperative nausea and vomiting in high-risk patients and may exacerbate the severity of nausea.[91]

The use of i.v. nonopioid analgesics and adjuvants, such as ketamine, α-2 agonists (notably dexmedetomidine), and lidocaine, has shown to significantly enhance recovery quality compared with placebo or other interventions.[4] Emphasising multimodal analgesia, which includes these agents as part of opioid-sparing strategies, can greatly improve postoperative pain relief[4] and reduce opioid consumption and complications, as observed in this study. This approach is highly recommended in the perioperative care of patients with obesity,[1,6] particularly for those enrolled in enhanced recovery programmes after surgery, which aim to optimise recovery outcomes and reduce hospital LOS.[1,11,92]

Strengths and limitations of the study

This ground-breaking network meta-analysis highlights the effectiveness of nonopioid i.v. analgesics and adjuvants in managing postoperative pain in patients with obesity. It underscores the importance of adopting multimodal analgesia strategies in clinical practice to reduce opioid consumption and improve postoperative outcomes. The study also emphasises the benefits of conducting an exhaustive literature review, which significantly reduces the risk of overlooking pivotal studies and ensures a robust dataset for analysis. Utilising a sophisticated network meta-analysis, it offers broader comparative insights than traditional methods that evaluate treatments in isolation. The research meticulously selects trials, focusing exclusively on RCTs of adults with obesity undergoing surgery, thus ensuring that the findings are highly relevant and directly applicable to this specific patient group. This targeted approach enhances the clarity and relevance of the results, providing a solid foundation for the conclusions drawn. Additionally, the integration of the GRADE assessment into our analysis represents a major strength of this research. This systematic method offers a precise evaluation of evidence certainty, thereby enhancing the reliability and applicability of the findings. By rigorously implementing the GRADE framework, the study offers readers a transparent view of the confidence level in the conclusions, aligning with best practices in evidence-based healthcare.

Several limitations are acknowledged in this study. Most of the RCTs analysed were conducted in single-centre settings, which might restrict the broader applicability of our findings to different clinical environments. There was also an uneven representation of evidence for various interventions, with some treatments less frequently studied. This uneven representation can impact the robustness and generalisability of our findings for these specific treatments. There is a need for more well-designed RCTs to strengthen the evidence base for these less frequently studied treatments, and a cautious interpretation of results for interventions with limited data is emphasised. Additionally, not all treatments were assessed at each time point in our analysis, potentially affecting the depth and reliability of our results. Significant heterogeneity among the RCTs could compromise their comparative effectiveness evaluation, with unexplored causes of this variance possibly limiting the understanding of the results. Important factors such as psychological aspects and pre-surgery chronic pain management were not considered, possibly affecting the accuracy of our conclusions regarding pain sensitivity. This research focused solely on the i.v. nonopioid analgesics and adjuvants discussed in the rationale for multimodal general anesthesia,[3] excluding drugs such as cyclooxygenase-2 inhibitors, nefopam, metamizole, and corticosteroids. Dexamethasone, however, has shown significant antiemetic effects without a morphine-sparing effect in the general population.[93] Although not included in our analysis, locoregional anaesthesia is a valuable strategy for reducing opioid consumption in patients with obesity.[10] Further investigation into the efficacy and safety of these drugs and locoregional strategies in patients with obesity could expand our knowledge of pain management. The study also did not explore the effects of drug dosage variations. In patients with obesity, physiological and anthropometric changes may significantly influence the pharmacokinetics of many drugs, necessitating precise dosing adjustments.[1] Although nonopioid analgesics and paracetamol typically do not require weight adjustments, and guidelines for drugs such as gabapentinoids and magnesium remain unclear, drugs such as ketamine, α-2 agonists, and lidocaine do require weight-based dosing to be effective and safe.[1,94] Addressing these issues in future research could greatly enhance our understanding of pain management's effectiveness and the impact of various interventions in postoperative care. This study has used various definitions of POPCs, which may be perceived as a limitation against the backdrop of the new consensus-based standards.[95] As numerous RCTs were conducted before the establishment of this consensus,[95] exact conformity was not possible. Nonetheless, the influence of those events not covered by the new criteria is negligible in our analysis, and the study endorses the adoption of these updated, stringent POPCs definitions in future research. Excluding non-RCTs, conference proceedings, and grey literature may increase the risk of publication bias, despite the clear advantages of focusing on peer-reviewed studies.

In conclusion, this systematic review and network meta-analysis confirms the effectiveness of nonopioid analgesics and adjuvants within a multimodal anaesthesia framework for patients with obesity. These agents, notably dexmedetomidine, ketamine, lidocaine, magnesium, and oral gabapentinoids, significantly reduced opioid use and minimised side effects such as postoperative nausea and vomiting. Additionally, the use of ketamine/esketamine lowered the risk of postoperative pulmonary complications, whereas dexmedetomidine and lidocaine decreased PACU and hospital stays. These findings support the adoption of nonopioid strategies to improve postoperative outcomes and reduce healthcare costs in obesity-related surgeries.

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Authors' contributions

Conceptualization: MC, PN
Methodology: all authors
Software: MC
Validation: all authors
Formal analysis: MC, ET
Investigation: all authors
Resources: all authors
Data curation: all authors
Original manuscript draft preparation: MC
Manuscript review and editing: all authors
Visualisation: MC, ET
Supervision: MC, PN
Project administration: MC, AB, and PN equally contributed to the manuscript.
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Declaration of interest

The authors declare no conflicts of interest.

Data availability statement

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2024.08.009.

References

1. Carron M, Safaee Fakhr B, Iepparielo G, Foletto M. Perioperative care of the obese patient. *Br J Surg* 2020; **107**: e39–55
2. Belcaid I, Eipe N. Perioperative pain management in morbid obesity. *Drugs* 2019; **79**: 1163–75
3. Brown EN, Pavone KJ, Naranjo M. Multimodal general anaesthesia: theory and practice. *Anesth Analg* 2018; **127**: 1246–58
4. Carron M, Tamburini E, Linassi F, Pettenuzzo T, Boscolo A, Navalesi P. Non-opioid analgesics and adjuvants after surgery in adults with obesity: systematic review with network meta-analysis of randomized controlled trials. *J Clin Med* 2024; **13**: 2100
5. Gupta K, Nagappa M, Prasad A, et al. Risk factors for opioid-induced respiratory depression in surgical patients: a systematic review and meta-analyses. *BMJ Open* 2018; **8**, e024086
6. Nightingale CE, Margarson MP, Shearer E, et al., Members of the Working Party. Peri-operative management of the obese surgical patient 2015: association of anaesthetists of great britain and Ireland society for obesity and bariatric anaesthesia. *Anaesthesia* 2015; **70**: 859–76
7. Ehsan Z, Mahmoud M, Shott SR, Amin RS, Ishman SL. The effects of anaesthesia and opioids on the upper airway: a systematic review. *Laryngoscope* 2016; **126**: 270–84
8. Fiore JF Jr, El-Kefraoui C, Chay MA, et al. Opioid versus opioid-free analgesia after surgical discharge: a systematic review and meta-analysis of randomised trials. *Lancet* 2022; **399**: 2280–93
9. Chou R, Gordon DB, de Leon-Casasola OA, et al. Management of postoperative pain: a clinical practice guideline from the American pain society, the American society of regional anaesthesia and pain medicine, and the American society of anesthesiologists' committee on regional anaesthesia, executive committee, and administrative council. *J Pain* 2016; **17**: 131–57
10. De Cassai A, Paganini G, Pettenuzzo T, et al. Single-shot regional anesthesia for bariatric surgery: a systematic review and network meta-analysis. *Obes Surg* 2023; **33**: 2687–94
11. Marinari G, Foletto M, Nagliati C, et al. Enhanced recovery after bariatric surgery: an Italian consensus statement. *Surg Endosc* 2022; **36**: 7171–86
12. Mechanick JI, Apovian C, Brethauer S, et al. Clinical practice guidelines for the perioperative nutrition, metabolic, and nonsurgical support of patients undergoing bariatric procedures - 2019 update: cosponsored by American association of clinical endocrinologists/American college of endocrinology, the obesity society, American society for metabolic and bariatric surgery, obesity medicine association, and American society of anesthesiologists. *Obesity (Silver Spring)* 2020; **28**: O1–58
13. Stenberg E, Dos Reis Falcão LF, O'Kane M, et al. Guidelines for perioperative care in bariatric surgery: enhanced Recovery after Surgery (ERAS) Society recommendations: a 2021 update. *World J Surg* 2022; **46**: 729–51
14. Bluth T, Serpa Neto A, Schultz MJ, et al., Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology. Effect of intraoperative high positive end-expiratory pressure (PEEP) with recruitment maneuvers vs low PEEP on Postoperative pulmonary complications in obese patients: a randomized clinical trial. *JAMA* 2019; **321**: 2292–305
15. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *BMJ* 2009; **339**: b2700
16. Miskovic A, Lumb AB. Postoperative pulmonary complications. *Br J Anaesth* 2017; **118**: 317–34
17. Kirmeier E, Eriksson LI, Lewald H, et al. Post-anaesthesia pulmonary complications after use of muscle relaxants (POPULAR): a multicentre, prospective observational study. *Lancet Respir Med* 2019; **7**: 129–40
18. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019; **366**: l4898
19. Puhan MA, Schünemann HJ, Murad MH, et al. A GRADE Working Group approach for rating the quality of treatment effect estimates from network meta-analysis. *BMJ* 2014; **349**: g5630
20. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol* 2005; **5**: 13
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60
22. Sterne JAC, Sutton AJ, Ioannidis JPA, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; **343**: d4002
23. Bakhamees HS, El-Halafawy YM, El-Kerdawy HM, Gouda NM, Altemyatt S. Effects of dexmedetomidine in morbidly obese patients undergoing laparoscopic gastric bypass. *Middle East J Anaesthesiol* 2007; **19**: 537–51
24. Kamal HM. Ketamine as an adjuvant to morphine for patient controlled analgesia in morbidly obese patients. *J Med Sci* 2008; **8**: 364–70
25. Tufanogullari B, White PF, Peixoto MP, et al. Dexmedetomidine infusion during laparoscopic bariatric surgery: the effect on recovery outcome variables. *Anesth Analg* 2008; **106**: 1741–8
26. Sollazzi L, Modesti C, Vitale F, et al. Preinductive use of clonidine and ketamine improves recovery and reduces postoperative pain after bariatric surgery. *Surg Obes Relat Dis* 2009; **5**: 67–71
27. Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. *Obes Surg* 2010; **20**: 1678–81
28. Hasanein R, El-Sayed W, Nabil N, Elsayed G. The effect of combined remifentanil and low dose ketamine infusion in patients undergoing laparoscopic gastric bypass. *Egypt J Anaesth* 2011; **27**: 255–60
29. De Oliveira GS Jr, Duncan K, Fitzgerald P, Nader A, Gould RW, McCarthy RJ. Systemic lidocaine to improve

quality of recovery after laparoscopic bariatric surgery: a randomized double-blinded placebo-controlled trial. *Obes Surg* 2014; **24**: 212–8
30. Hassani V, Pazouki A, Nikoubakht N, Chaichian S, Sayarifard A, Shakib Khankandi A. The effect of gabapentin on reducing pain after laparoscopic gastric bypass surgery in patients with morbid obesity: a randomized clinical trial. *Anesth Pain Med* 2015; **5**, e22372
31. Salama AK, Abdallah NM. Multimodal analgesia with pregabalin and dexmedetomidine in morbidly obese patients undergoing laparoscopic sleeve gastrectomy: a prospective randomized double blind placebo controlled study. *Egypt J Anaesth* 2016; **32**: 293–8
32. El Chaar M, Stoltzfus J, Claros L, Wasylik T. IV Acetaminophen results in lower hospital costs and emergency room visits following bariatric surgery: a double-blind, prospective, randomized trial in a single accredited bariatric center. *J Gastrointest Surg* 2016; **20**: 715–24
33. Sherif AA, Elsersy HE. The impact of dexmedetomidine or xylocaine continuous infusion on opioid consumption and recovery after laparoscopic sleeve gastrectomy. *Minerva Anestesiol* 2017; **83**: 1274–82
34. Cooke FE, Samuels JD, Pomp A, et al. A randomized, double-blind, placebo-controlled trial of intravenous acetaminophen on hospital length of stay in obese individuals undergoing sleeve gastrectomy. *Obes Surg* 2018; **28**: 2998–3006
35. Erdogan Kayhan G, Sanli M, Ozgul U, Kirteke R, Yologlu S. Comparison of intravenous ibuprofen and acetaminophen for postoperative multimodal pain management in bariatric surgery: a randomized controlled trial. *J Clin Anesth* 2018; **50**: 5–11
36. Lange M, Lee CW, Knisely T, Perla S, Barber K, Kia M. Efficacy of intravenous acetaminophen in length of stay and postoperative pain control in laparoscopic Roux-en-Y gastric bypass surgery patients. *Bariatr Surg Pract Patient Care* 2018; **13**: 103–8
37. Martins MJ, Martins CPMO, Castro-Alves LJ, et al. Pregabalin to improve postoperative recovery in bariatric surgery: a parallel, randomized, double-blinded, placebo-controlled study. *J Pain Res* 2018; **11**: 2407–15
38. Mostafa RH, Ibrahim IM, Ayoub AH. Effect of perioperative dexmedetomidine infusion on blood glucose levels in non-diabetic morbid obese patients undergoing laparoscopic bariatric surgery. *Egypt J Anaesth* 2018; **34**: 75–81
39. Rupniewska-Ladyko A, Malec-Milewska M, Kraszewska E, Pirozynski M. Gabapentin before laparoscopic sleeve gastrectomy reduces postoperative oxycodone consumption in obese patients: a randomized double-blind placebo-controlled trial. *Minerva Anestesiol* 2018; **84**: 565–71
40. Ciftci B, Ekinci M, Celik EC, et al. Comparison of Intravenous ibuprofen and paracetamol for postoperative pain management after laparoscopic sleeve gastrectomy. a randomized controlled study. *Obes Surg* 2019; **29**: 765–70
41. El Mourad MB, Arafa SK. Effect of intravenous versus intraperitoneal magnesium sulfate on hemodynamic parameters and postoperative analgesia during laparoscopic sleeve gastrectomy-a prospective randomized study. *J Anaesthesiol Clin Pharmacol* 2019; **35**: 242–7
42. Khan MU, Bamehriz FY, Aqil M, Dammas FA, Fadin A, Khokhar RS. The effect of gabapentin on postoperative pain, morphine sparing effect and preoperative anxiety in patients going for sleeve gastrectomy surgical procedure. *J Coll Physicians Surg Pak* 2019; **29**: 697–701
43. Kizilcik N, Koner O. Magnesium sulfate reduced opioid consumption in obese patients undergoing sleeve gastrectomy: a prospective, randomized clinical trial. *Obes Surg* 2018; **28**: 2783–8
44. Ranganathan P, Ritchie MK, Ellison MB, Petrone A, Heiraty P, Tabone LE. A randomized control trial using intraoperative dexmedetomidine during Roux-en-Y gastric bypass surgery to reduce postoperative pain and narcotic use. *Surg Obes Relat Dis* 2019; **15**: 588–94
45. Wang J, Echevarria GC, Doan L, et al. Effects of a single subanaesthetic dose of ketamine on pain and mood after laparoscopic bariatric surgery: a randomised double-blind placebo controlled study. *Eur J Anaesthesiol* 2019; **36**: 16–24
46. de Oliveira CMB, Coelho LMG, Valadão JA, et al. Assessment of the effect of perioperative venous lidocaine on the intensity of pain and IL-6 concentration after laparoscopic gastroplasty. *Obes Surg* 2020; **30**: 3912–8
47. Jabbour H, Jabbour K, Abi Lutfallah A, et al. Magnesium and ketamine reduce early morphine consumption after open bariatric surgery: a prospective randomized double-blind study. *Obes Surg* 2020; **30**: 1452–8
48. Kasputytė G, Karbonskienė A, Macas A, Maleckas A. Role of ketamine in multimodal analgesia protocol for bariatric surgery. *Medicina (Kaunas)* 2020; **56**: 96
49. Sakata RK, de Lima RC, Valadão JA, et al. Randomized, double-blind study of the effect of intraoperative intravenous lidocaine on the opioid consumption and criteria for hospital discharge after bariatric surgery. *Obes Surg* 2020; **30**: 1189–93
50. Adhikary SD, Thiruvenkatarajan V, McFadden A, Liu WM, Mets B, Rogers A. Analgesic efficacy of ketamine and magnesium after laparoscopic sleeve gastrectomy: a randomized, double-blind, placebo-controlled trial. *J Clin Anesth* 2021; **68**, 110097
51. Mehta SD, Smyth D, Vasilopoulos T, Friedman J, Sappenfield JW, Alex G. Ketamine infusion reduces narcotic requirements following gastric bypass surgery: a randomized controlled trial. *Surg Obes Relat Dis* 2021; **17**: 737–43
52. Plass F, Nicolle C, Zamparini M, et al. Effect of intraoperative intravenous lidocaine on opioid consumption after bariatric surgery: a prospective, randomised, blinded, placebo-controlled study. *Anaesthesia* 2021; **76**: 189–98
53. Seman MT, Malan SH, Buras MR, et al. Low-dose ketamine infusion for perioperative pain management in patients undergoing laparoscopic gastric bypass: a prospective randomized controlled trial. *Anesthesiol Res Pract* 2021; **2021**, 5520517
54. Sun J, Wang S, Wang J, Gao X, Wang G. Effect of intravenous infusion of lidocaine compared with ultrasound-guided transverse abdominal plane block on the quality of postoperative recovery in patients undergoing laparoscopic bariatric surgery. *Drug Des Devel Ther* 2022; **16**: 739–48
55. Ustun YB, Turunc E, Ozbalci GS, et al. Comparison of ketamine, dexmedetomidine and lidocaine in multimodal analgesia management following sleeve gastrectomy surgery: a randomized double-blind trial. *J Perianesth Nurs* 2022; **37**: 820–6
56. Ahmed AYI, Afifi MKMA, Arida EAE, Abdelhady MM. Effect of magnesium levels on mean tissue perfusion during and after bariatric surgeries: a randomised control trial. *Egypt J Anaesth* 2023; **39**: 502–10
57. Khalil BNM, Elderh MSH, Khaja MAR, El-Shaer AN, Ali BEEH, Taeimah MOA. Perioperative use of ketamine

infusion versus dexmedetomidine infusion for analgesia in obese patients undergoing bariatric surgery: a double-blinded three-armed randomized controlled trial. *BMC Anesthesiol* 2023; **23**: 108
58. Yurttas T, Djurdjevic M, Schnider TW, Filipovic M. Analgesic efficacy of systemic lidocaine using lean body mass based dosing regimen versus placebo in bariatric surgery: a prospective, randomised, double-blind, placebo-controlled, single-centre study. *Br J Anaesth* 2023; **131**: 122–9
59. Zhang J, Wang F, Dang J, et al. Effect of intraoperative infusion of esketamine on quality of postoperative recovery in patients undergoing laparoscopic bariatric surgery: a randomized controlled trial. *Pain Ther* 2023; **12**: 979–92
60. Albarrak AA. Safety of non-steroidal anti-inflammatory drugs as part of enhanced recovery after laparoscopic sleeve gastrectomy – a systematic review and meta-analysis. *Obes Surg* 2024; **34**: 643–52
61. Lee Y, Yu J, Doumouras AG, et al. Intravenous acetaminophen versus placebo in post-bariatric surgery multimodal pain management: a meta-analysis of randomized controlled trials. *Obes Surg* 2019; **29**: 1420–8
62. Hung KC, Wu SC, Chang PC, et al. Impact of intraoperative ketamine on postoperative analgesic requirement following bariatric surgery: a meta-analysis of randomized controlled trials. *Obes Surg* 2021; **31**: 5446–57
63. Singh PM, Panwar R, Borle A, Mulier JP, Sinha A, Goudra B. Perioperative analgesic profile of dexmedetomidine infusions in morbidly obese undergoing bariatric surgery: a meta-analysis and trial sequential analysis. *Surg Obes Relat Dis* 2017; **13**: 1434–46
64. Tian C, Malhan RS, Deng SX, et al. Benefits of dexmedetomidine on postoperative analgesia after bariatric surgery. *Minerva Anestesiol* 2022; **88**: 173–83
65. Sanchez Munoz MC, De Kock M, Forget P. What is the place of clonidine in anaesthesia? Systematic review and meta-analyses of randomized controlled trials. *J Clin Anesth* 2017; **38**: 140–53
66. Hung KC, Chang YJ, Chen IW, Chang YP, Chiu SF, Sun CK. Efficacy of intraoperative intravenous lidocaine for postoperative analgesia following bariatric surgery: a meta-analysis of randomized controlled studies. *Surg Obes Relat Dis* 2022; **18**: 135–47
67. De Oliveira GS Jr, Castro-Alves LJ, Khan JH, McCarthy RJ. Perioperative systemic magnesium to minimize postoperative pain: a meta-analysis of randomized controlled trials. *Anesthesiology* 2013; **119**: 178–90
68. Albrecht E, Kirkham KR, Liu SS, Brull R. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. *Anaesthesia* 2013; **68**: 79–90
69. Carron M, Ieppariello G, Linassi F, Navalesi P. Ketamine and magnesium: a successful combination for bariatric surgery. *Obes Surg* 2020; **30**: 4612–4
70. Hung KC, Wu SC, Chiang MH, et al. Analgesic efficacy of gabapentin and pregabalin in patients undergoing laparoscopic bariatric surgeries: a systematic review and meta-analysis. *Obes Surg* 2022; **32**: 2734–43
71. Xuan C, Yan W, Wang D, et al. Efficacy of preemptive analgesia treatments for the management of postoperative pain: a network meta-analysis. *Br J Anaesth* 2022; **129**: 946–58
72. Chincholkar M. Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review. *Br J Anaesth* 2018; **120**: 1315–34
73. Zhao Y, He J, Yu N, Jia C, Wang S. Mechanisms of dexmedetomidine in neuropathic pain. *Front Neurosci* 2020; **14**: 330
74. Mantz J, Josserand J, Hamada S. Dexmedetomidine: new insights. *Eur J Anaesthesiol* 2011; **28**: 3–6
75. Wang X, Lin C, Lan L, Liu J. Perioperative intravenous S-ketamine for acute postoperative pain in adults: a systematic review and meta-analysis. *J Clin Anesth* 2021; **68**, 110071
76. Mion G, Himmelseher S. Esketamine: less drowsiness, more analgesia. *Anesth Analg* 2024; **139**: 78–91
77. Andrade C. Ketamine for depression, 4: in what dose, at what rate, by what route, for how long, and at what frequency? *J Clin Psychiatry* 2017; **78**: e852–7
78. Górska N, Cubała WJ, Słupski J, Gałuszko-Węgielnik M. Ketamine and magnesium common pathway of antidepressant action. *Magnes Res* 2018; **31**: 33–8
79. Bahji A, Zarate CA, Vazquez GH. Efficacy and safety of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *Expert Opin Drug Saf* 2022; **21**: 853–66
80. Bahji A, Vazquez GH, Zarate Jr CA. Comparative efficacy of racemic ketamine and esketamine for depression: a systematic review and meta-analysis. *J Affect Disord* 2021; **278**: 542–55
81. Hung KC, Kao CL, Ho CN, et al. The impact of perioperative ketamine or esketamine on the subjective quality of recovery after surgery: a meta-analysis of randomised controlled trials. *Br J Anaesth* 2024; **132**: 1293–303
82. Iacob E, Hagn EE, Sindt J, et al. Tertiary care clinical experience with intravenous lidocaine infusions for the treatment of chronic pain. *Pain Med* 2018; **19**: 1245–53
83. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. *Br J Pain* 2020; **14**: 104–14
84. Pattinson KT. Opioids and the control of respiration. *Br J Anaesth* 2008; **100**: 747–58
85. Jonkman K, van Rijnsoever E, Olofsen E, et al. Esketamine counters opioid-induced respiratory depression. *Br J Anaesth* 2018; **120**: 1117–27
86. Song Y, Zhu J, Dong Z, Wang C, Xiao J, Yang W. Incidence and risk factors of postoperative nausea and vomiting following laparoscopic sleeve gastrectomy and its relationship with Helicobacter pylori: a propensity score matching analysis. *Front Endocrinol (Lausanne)* 2023; **14**, 1102017
87. Jin S, Liang DD, Chen C, Zhang M, Wang J. Dexmedetomidine prevent postoperative nausea and vomiting on patients during general anaesthesia: a PRISMA-compliant meta-analysis of randomized controlled trials. *Medicine (Baltimore)* 2017; **96**, e5770
88. Chang PC, Huang IY, Liu SD, et al. Perioperative dexmedetomidine infusion improves perioperative care of bariatric-metabolic surgery: a single center experience with meta-analysis. *Obes Surg* 2024; **34**: 416–28
89. Chen IW, Kao CL, Hung KC. Perioperative dexmedetomidine infusion and postoperative nausea and vomiting: a meta-regression analysis. *Obes Surg* 2024; **34**: 1942–3
90. Weibel S, Jelting Y, Pace NL, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. *Cochrane Database Syst Rev* 2018; **6**: CD009642
91. Song JW, Shim JK, Song Y, Yang SY, Park SJ, Kwak YL. Effect of ketamine as an adjunct to intravenous patient-

controlled analgesia, in patients at high risk of postoperative nausea and vomiting undergoing lumbar spinal surgery. *Br J Anaesth* 2013; **111**: 630–5

92. Ahmed OS, Rogers AC, Bolger JC, Mastrosimone A, Robb WB. Meta-analysis of enhanced recovery protocols in bariatric surgery. *J Gastrointest Surg* 2018; **22**: 964–72
93. Martinez V, Beloeil H, Marret E, Fletcher D, Ravaud P, Trinquart L. Non-opioid analgesics in adults after major surgery: systematic review with network meta-analysis of randomized trials. *Br J Anaesth* 2017; **118**: 22–31
94. Erstad BL, Barletta JF. Drug dosing in the critically ill obese patient-a focus on sedation, analgesia, and delirium. *Crit Care* 2020; **24**: 315
95. Abbott TEF, Fowler AJ, Pelosi P, et al. A systematic review and consensus definitions for standardised end-points in perioperative medicine: pulmonary complications. *Br J Anaesth* 2018; **120**: 1066–79

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