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Risk of Opioid-induced Nausea and Vomiting after Abdominal Hysterectomy: Systematic Review and Meta-analysis

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Abstract

Background

Abdominal hysterectomy is associated with moderate-to-severe postoperative pain, and while opioids remain the primary treatment, they frequently induce opioid-associated postoperative nausea and vomiting (O-PONV). Opioid-sparing multimodal therapies are expected to mitigate this dose-dependent risk, but direct evidence comparing their emetogenic profiles remains limited and heterogeneous. To address this, a systematic review comprising both pairwise and network meta-analyses was conducted to evaluate O-PONV incidence across different analgesic strategies for abdominal hysterectomy. The risk between morphine monotherapy and morphine-based multimodal therapies was compared.

Methods

A systematic search of PubMed, EMBASE, the Cochrane Library, and RISS was conducted in March 2026 according to PICO-based criteria. Eligible studies were randomized controlled trials (RCTs) of patients undergoing abdominal hysterectomy that compared postoperative opioid-based analgesic regimens and reported postoperative nausea and vomiting (PONV) within 24 hours. Risk of bias was evaluated using the Cochrane RoB 2 tool. Pairwise meta-analysis estimated pooled odds ratio with 95% confidence intervals, and a frequentist network meta-analysis compared individual treatment regimens and ranked them based on P-scores.

Results

A total of 10 RCTs involving 711 patients were included that compared morphine monotherapy with morphine-based multimodal regimens. In the pairwise meta-analysis, multimodal therapy showed a significantly lower risk of nausea or vomiting than monotherapy (OR, 0.561; 95% CI, 0.406–0.776; $P < 0.001$; $I^2 = 0\%$). In the network meta-analysis, morphine plus tenoxicam regimen ranked highest according to the P-score and was associated with a significantly lower risk of postoperative nausea or vomiting than morphine monotherapy and morphine plus acetaminophen. Separate analyses of postoperative nausea and postoperative vomiting also demonstrated significantly lower risks with multimodal therapy than with morphine monotherapy. Mean morphine consumption was significantly lower with multimodal therapies than with monotherapy (35.22mg vs. 44.28mg; $P < 0.0001$).

Conclusions

Compared with monotherapy, morphine-based multimodal therapies were associated with a significantly lower risk of O-PONV after abdominal hysterectomy, with morphine plus tenoxicam exhibiting the lowest risk. Further studies incorporating a broader range of recent clinical trials are warranted to reconfirm these associations and strengthen the evidence base.

Background

Hysterectomy is one of the most frequently performed gynecological procedures worldwide [1–3]. It addresses a variety of indications, from benign conditions like uterine fibroids and endometriosis to advanced pathologies such

as gynecological cancers and pelvic support disorders [4]. Although type of surgical approach varies, abdominal hysterectomy is the most traditional technique that enables the comprehensive management of malignancies [4].

As with any major surgery, postoperative pain management following a hysterectomy remains a significant clinical concern. The intensity of post-surgical pain typically ranges from moderate to severe and is profoundly influenced by patient-specific factors [5]. Optimizing postoperative analgesia is critical [6]; it not only enhances patient comfort but also facilitates functional recovery and reduces the risk of postoperative complications [5]. Historically, opioids have been the mainstay of postoperative pain control; however, their clinical use is closely associated with a range of adverse effects, with postoperative nausea and vomiting (PONV) being among the most distressing to patients [7].

Given that women undergoing abdominal hysterectomy already carry an intrinsically high risk of PONV, the administration of postoperative opioids further compounds this risk as a significant, modifiable factor [8]. Beyond patient discomfort, PONV can lead to dehydration, electrolyte imbalance, delayed ambulation, or, in severe cases, critical complications such as wound dehiscence and prolonged hospital stay, escalating healthcare costs [9].

To mitigate this burden, opioid-sparing multimodal strategies have become a central component of enhanced recovery. By combining non-opioid analgesics, multimodal therapies provide effective pain relief while minimizing total opioid consumption, thereby lowering the incidence of dose-dependent opioid-associated PONV (O-PONV) and enhancing recovery quality [10].

Despite the physiological rationale, evidence directly comparing the emetogenic safety of opioid monotherapy versus multimodal therapies specifically after abdominal hysterectomy remains limited. Existing studies are not only highly heterogeneous in their analgesic protocols, but they also rarely report O-PONV as a primary outcome in dedicated abdominal hysterectomy populations [11]. Therefore, a targeted synthesis focusing on O-PONV as an outcome is warranted to determine the safety advantages of multimodal strategies. Accordingly, we conducted a systematic review comprising both pairwise and network meta-analyses to evaluate the incidence of O-PONV across different analgesic strategies for abdominal hysterectomy. Our primary focus was comparing the risk of O-PONV between opioid monotherapy and various opioid-based multimodal therapies.

Methods

Eligibility criteria

This systematic review and meta-analysis followed the guidelines provided by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Eligible studies were randomized controlled trials (RCTs) based on the following PICO framework:

Population (P): women who underwent abdominal hysterectomy

Intervention (I): opioid-based multimodal therapies for postoperative pain management

Comparison (C): opioid analgesics for postoperative pain management

Outcome (O): postoperative nausea or vomiting

To ensure consistency in study selection, postoperative analgesic use was operationally defined as analgesic administration initiated at wound closure, immediately after surgery, or continued during the postoperative period.

Opioid-based multimodal therapies included pharmacological agents administered in combination with opioids for postoperative pain management. Only studies published in English were included.

Search strategy and study selection

A systematic search of PubMed (NLM®), EMBASE (OvidSP), the Cochrane Library (Cochrane), and RISS (Korea Education and Research Information Service) was conducted in March 2026 according to the search strategy presented in Table S1. The search strategy combined terms related to opioids, nausea, vomiting, and abdominal hysterectomy. Among the identified articles, duplicates were removed using the bibliographic software EndNote 20 (Clarivate, Philadelphia, PA, USA) to facilitate systematic screening and identification.

Two authors (S.C. and J.K.) independently screened the titles and abstracts of the retrieved records. The full texts of potentially eligible articles were then reviewed to determine final eligibility according to the predefined PICO-based inclusion criteria. Any disagreements between the authors were resolved by discussion or by a third author (E.L.) until a consensus was reached.

Data extraction and outcome measures

Two authors (S.C. and S.S.) independently extracted the data, and a third reviewer (E.L.) verified the extracted information for accuracy. Extracted information included study characteristics, pain management interventions (e.g., type of opioid regimen, total dose, and route of administration), outcome data, morphine consumption and antiemetic use. Three-arm studies were divided into two pairwise comparisons, each comparing a multimodal therapies with monotherapy.

The primary outcome was 24-hour nausea or vomiting incidence. When nausea and vomiting incidences were reported separately, the higher incidence was used to represent postoperative nausea or vomiting. For studies reporting one component as incidence and the other as a severity score, the incidence-based outcome was preferentially extracted. Additional outcome measures included postoperative nausea incidence and postoperative vomiting incidence.

Risk of bias assessment

The risk of bias of the included studies was assessed using the Cochrane Risk of Bias 2 tool. The assessment covered bias arising from the randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain was judged as having a low risk of bias, some concerns, or a high risk of bias, from which an overall risk of bias judgement was derived. Independent risk of bias assessments was performed by three authors (S.S., S.C., and K.B.), and any discrepancies were resolved through discussions.

Statistical analysis

Effect estimates were calculated as odds ratios (ORs) with 95% confidence intervals (CIs), and heterogeneity was assessed by the I^2 statistic. Pairwise meta-analyses were performed with Comprehensive Meta-Analysis Software (CMA) using a random-effects model. Sensitivity analyses and publication bias assessments were additionally completed in CMA. A frequentist network meta-analysis (NMA) was conducted using the “netmeta” package in R

version 4.4.2 (The R Foundation for Statistical Computing) to compare and rank individual treatment regimens based on P-scores. Sensitivity analyses included separate analyses of postoperative nausea and postoperative vomiting, as well as leave-one-out analyses in which one study was excluded at a time. Publication bias was evaluated using funnel plots.

Results

Study selection

A total of 1,317 relevant articles were identified through our literature search. After excluding 353 duplicate records, 964 underwent title and abstract screening. Following full-text assessment of 180 articles for eligibility, 10 studies were ultimately included in the meta-analysis (Fig. 1).

Study characteristics

The 10 included RCTs involved a total of 711 participants. In all studies, the opioid monotherapy group received morphine. Multimodal therapies consisted of morphine combined with nonsteroidal anti-inflammatory drugs (NSAIDs), acetaminophen, pregabalin, gabapentin, ketamine, bupivacaine, or duloxetine (Table. 1). The pooled mean morphine consumption was 44.28 mg (SD, 27.77) in the monotherapy group and 35.22 mg (SD, 23.34) in the multimodal therapy group ($P < 0.0001$).

Table 1
Characteristics of included studies

Study	Number of patients	Intervention	Treatment details	Nausea or vomiting Outcome	Morphine consumption (mg) [a]	Antiemetic use
Blackburn, 1995 (UK) [12]	30	Ketorolac	IV infusion: 1 mg/ml (total 120mg)	Incidence: N 19, V 11	43 (17)	Metoclopramide, prochlorperazine, or cyclizine [b]
		Morphine	PCA: maximum 1 mg every 5 min			
	29	Morphine	PCA: maximum 1 mg every 5 min	Incidence: N 18, V 11	55 (22)	
Castro-Alves, 2016 (Brazil) [13]	31	Duloxetine	PO 60mg (total 120 mg)	Incidence: N 11, V 3	1 (0–5)	Ondansetron 4mg
		Morphine	IV: 1–2 mg every 15 min			
	32	Morphine	IV: 1–2 mg every 15 min	Incidence: N 18, V 6	5.5 (0.5-9)	
Cobby, 1999 (UK) [14]	24	Paracetamol	Rectal 1.3 g (total 3.9 g)	NRS [c]: N 28 (0–90) Incidence: V 5 (21%)	35 (20.4)	Prochlorperazine 12.5 mg as required
		Morphine	PCA: 1 mg with 5-min lockout, no basal infusion			
	20	Diclofenac	Rectal 50 mg (total 150 mg)	NRS [c]: N 20 (0–90) Incidence: V 2 (10%)	32.7 (27.4)	
		Morphine	PCA: 1 mg with 5-min lockout, no basal infusion			
	21	Morphine	PCA: 1mg with 5-min lockout, no basal infusion	NRS [c]: N 40 (0-100) Incidence: V 3 (14%)	54.9 (28.3)	
Dierking, 2014 (Denmark) [15]	39	Gabapentin	PO: initial dose 1200 mg, 600 mg every 8 hours (total 3000 mg)	Incidence: N 12 (31%), V 18 (46%)	63 (53–88)	Ondansetron 4 mg as required

IV: intravenous; PO: Per Os; PCA: patient controlled analgesia; IQR: interquartile range; N: nausea; V: vomiting; NV: nausea or vomiting; NRS: Numerical Rating Scale; [a] Morphine consumption (mg) are expressed as mean (SD) or median (IQR); [b] Regimen and route of administration not provided; [c] NRS, mean (range); [d] NV score (5-point), mean (SD); [e] PONV (NRS 0–5), mean (SD); [f] Linear analogue scale (0-100mm), median (interquartile range)

Study	Number of patients	Intervention	Treatment details	Nausea or vomiting Outcome	Morphine consumption (mg) [a]	Antiemetic use
		Morphine	PCA: bolus 2.5 mg, 10-min lockout			
	32	Morphine	PCA: bolus 2.5 mg, 10-min lockout	Incidence: N 11 (35%), V 15 (47%)	43 (28–60)	
Gunusen, 2012 (Türkiye) [16]	40	Paracetamol	IV infusion: 1 g every 6 hours	Incidence: N 24 (60%), V 16 (40%)	64.6 (19.6)	Ondansetron 8 mg
		Morphine	PCA: 0.3 mg/ml, 15-min lockout, no basal infusion			
	40	Tenoxicam	IV infusion: 20 mg every 6 hours	Incidence: N 16 (40%), V 10 (25%)	44.8 (17.4)	
		Morphine	PCA: 0.3 mg/ml, 15-min lockout, no basal infusion			
	40	Morphine	PCA: 0.3 mg/ml, 15-min lockout, no basal infusion	Incidence: N 27 (67.5%), V 15 (37.5%)	69.2 (22.1)	
Hercock, 1999 (New Zealand) [17]	24	Ketamine, Morphine	PCA: 1 mg/ml, 6-min lockout, maximum 10 mg/h, no basal infusion	Score [d]: NV 2.1 (1.15) Incidence: V 5/24	34.5 (15.2)	Metoclopramide 10 mg, cyclizine 50 mg, and ondansetron 4 mg, if required
	25	Morphine	PCA: 1mg/ml, 6-min lockout, maximum 10mg/h, no basal infusion	Score [d]: NV 2.3 (0.95) Incidence: V 11/25	33 (16.0)	
Jarruwale, 2016 (Thailand) [18]	31	Bupivacaine	Intraperitoneal: 0.25% 60ml	NRS [e]: NV 0.35 (0.839) Incidence: V 5	16.13 (8.9)	Not specified
		Morphine	PCA: loading dose 3mg, bolus 1mg, 5-min lockout			

IV: intravenous; PO: Per Os; PCA: patient controlled analgesia; IQR: interquartile range; N: nausea; V: vomiting; NV: nausea or vomiting; NRS: Numerical Rating Scale; [a] Morphine consumption (mg) are expressed as mean (SD) or median (IQR); [b] Regimen and route of administration not provided; [c] NRS, mean (range); [d] NV score (5-point), mean (SD); [e] PONV (NRS 0–5), mean (SD); [f] Linear analogue scale (0-100mm), median (interquartile range)

Study	Number of patients	Intervention	Treatment details	Nausea or vomiting Outcome	Morphine consumption (mg) [a]	Antiemetic use
	31	Morphine	PCA: loading dose 3mg, bolus 1mg, 5-min lockout	NRS [e]: NV 0.26 (0.631) Incidence: V 8	25.03 (12.5)	
Lin, 2009 (China) [19]	50	Dexmedetomidine Morphine	PCA: 1 mg/ml, 1 ml bolus, 5-min lockout, no basal infusion	Incidence: N 30 (60%), V 15 (32%)	32.8 (12.4)	Prochlorperazine 10 mg IV
	48	Morphine	PCA: 1 mg/ml, 1 ml bolus, 5-min lockout, no basal infusion	Incidence: N 33 (69%), V 18 (38%)	23.3 (10)	
Ng, 2002 (UK) [20]	18	Diclofenac	Rectal: 75 mg every 12 hours (total 300 mg)	Score [f]: N 14 (0–53) Incidence: V 0	31 (14–65)	Not specified
		Morphine	PCA [b] (settings not specified)			
	16	Morphine	PCA [b] (settings not specified)	Score [f]: N 64 (30–109) Incidence: V 0	59 (45–85)	
Yucel, 2011 (Türkiye) [21]	30	Pregabalin, Morphine	PO: 150 mg every 12 hours (total 300 mg) PCA: 2 ml bolus, 15-min lockout, 4h-limit, no basal infusion	Incidence: NV 2	40.80 (3.42)	Metoclopramide 10 mg IV
	30	Pregabalin, Morphine	PO: 300 mg every 12 hours (total 600 mg) PCA: 2 ml bolus, 15-min lockout, 4h-limit, no basal infusion	Incidence: NV 5	33.79 (3.12)	

IV: intravenous; PO: Per Os; PCA: patient controlled analgesia; IQR: interquartile range; N: nausea; V: vomiting; NV: nausea or vomiting; NRS: Numerical Rating Scale; [a] Morphine consumption (mg) are expressed as mean (SD) or median (IQR); [b] Regimen and route of administration not provided; [c] NRS, mean (range); [d] NV score (5-point), mean (SD); [e] PONV (NRS 0–5), mean (SD); [f] Linear analogue scale (0-100mm), median (interquartile range)

Study	Number of patients	Intervention	Treatment details	Nausea or vomiting Outcome	Morphine consumption (mg) [a]	Antiemetic use
	30	Morphine	PCA: 2 ml bolus, 15-min lockout, 4h-limit, no basal infusion	Incidence: NV 7	46.97 (6.67)	

IV: intravenous; PO: Per Os; PCA: patient controlled analgesia; IQR: interquartile range; N: nausea; V: vomiting; NV: nausea or vomiting; NRS: Numerical Rating Scale; [a] Morphine consumption (mg) are expressed as mean (SD) or median (IQR); [b] Regimen and route of administration not provided; [c] NRS, mean (range); [d] NV score (5-point), mean (SD); [e] PONV (NRS 0–5), mean (SD); [f] Linear analogue scale (0-100mm), median (interquartile range)

Risk of bias assessment

Three out of the ten studies (30%) were judged as having some concerns, while the remaining seven were rated as having a low risk of bias. These concerns arose from the selection of the reported result (domain 5) in two studies and the randomization process (domain 1) in one study (Fig. 2).

Pairwise meta-analysis

Postoperative nausea or vomiting was analyzed using both conventional and network meta-analyses. Among the 10 eligible studies, one study with zero events in both groups was excluded because an odds ratio could not be estimated. Consequently, the pairwise meta-analysis included 11 pairwise comparisons from nine studies. Multimodal therapy was associated with a significantly lower risk of 24-hour nausea or vomiting than opioid monotherapy (OR, 0.561; 95% CI, 0.406–0.776; $P < 0.001$; $I^2 = 0\%$). Although two studies showed an effect estimate in the opposite direction, the pooled estimate favored multimodal therapy (Fig. 3). The funnel plot showed no clear asymmetry, suggesting no substantial publication bias (Fig. S1).

Pairwise meta-analyses were also conducted for postoperative nausea and postoperative vomiting as individual outcomes. Six pairwise comparisons from five studies were included to analyze nausea incidence and 10 pairwise comparisons from eight studies were included to analyze vomiting incidence. In both analyses, multimodal therapy showed significantly lower risks of postoperative nausea (OR, 0.593; 95% CI, 0.403–0.873; $P = 0.008$; $I^2 = 0\%$) and postoperative vomiting (OR, 0.677; 95% CI, 0.477–0.962; $P = 0.029$; $I^2 = 0\%$) than morphine monotherapy (Fig. 4).

Network meta-analysis

The league table presents odds ratios with 95% confidence intervals for all treatment comparisons. Based on P-scores, morphine plus tenoxicam ranked highest, and morphine monotherapy ranked lowest. Morphine plus tenoxicam was associated with a significantly lower risk of 24-hour nausea or vomiting than morphine plus acetaminophen and morphine monotherapy (Fig. 5).

Discussion

This systematic review and meta-analysis, included 10 randomized controlled trials involving 711 participants and examined the risk of O-PONV with morphine monotherapy versus morphine-based multimodal analgesic regimens following abdominal hysterectomy. No trial was judged to be at high risk of bias, although three studies had some

concerns. Overall, multimodal regimens significantly reduced the risk of O-PONV compared with morphine monotherapy, with morphine plus tenoxicam ranking highest for risk reduction. Sensitivity analyses supported the robustness of these findings.

These findings have clinical relevance because PONV can affect patient satisfaction, early mobilization, and resumption of oral intake [7, 9]. Given the dose-dependent nature of opioid-induced nausea and vomiting [22, 23], reducing cumulative opioid exposure through multimodal analgesia may help explain the observed reduction in O-PONV. Our findings are consistent with clinical practice guidelines recommending multimodal analgesia [24, 25] and provide further support for its use in postoperative pain management. By reducing opioid-related adverse effects, these strategies may also facilitate recovery and reduce hospital resource use [22, 23], although these broader benefits require direct evaluation.

The ranking of morphine plus tenoxicam warrants further consideration. Tenoxicam has a mean half-life of approximately 72 hours [26], compared with 2–12 hours for the other nine non-opioid agents evaluated in this review [27]. Given its longer half-life, a single dose of tenoxicam may remain pharmacologically active through the first 24 postoperative hours. Differences in adverse-effect profiles may also be relevant when selecting an adjunct. Centrally acting agents, such as ketamine, gabapentinoids, duloxetine, and dexmedetomidine can cause sedation, dizziness, or psychomimetic symptoms. However, the present analysis does not establish the overall comparative safety of tenoxicam or confirm that its pharmacological properties explain its ranking. Its availability and regulatory status may also influence the applicability of these findings across clinical settings [26].

This study has several limitations. First, the definition of the primary outcome varied across the included studies. Some reported nausea and vomiting as a combined outcome [12, 13, 15, 16, 19, 21], whereas others reported vomiting incidence and assessed nausea using a continuous scale [14, 17, 18, 20]. We conducted separate sensitivity analyses for nausea and vomiting to assess the robustness of our findings, but differences in outcome measurement may still limit comparability. Second, cumulative morphine doses varied across studies, potentially influencing emetic risk because O-PONV is dose-dependent [28]. Third, the use of antiemetics might have masked the effectiveness of multimodal regimens on O-PONV. Among the included studies, antiemetics were administered but only two studies did not report any specific antiemetic use [18, 20]. These differences complicate the interpretation of the observed treatment effects.

Although pooled morphine consumption was higher in the monotherapy group, this finding alone does not establish the extent to which reduced opioid exposure accounted for the lower risk of O-PONV. The results should therefore be interpreted in the context of variations in dosing and perioperative protocols. Larger studies using standardized outcome definitions and detailed reporting of opioid and antiemetic exposure are needed to clarify these relationships.

Conclusions

Morphine-based multimodal analgesic regimens significantly reduced the risk of O-PONV compared with morphine monotherapy following abdominal hysterectomy. Findings were consistent when nausea and vomiting were evaluated separately and were supported by sensitivity analyses. Morphine plus tenoxicam ranked highest for risk reduction, although this ranking alone does not establish superiority over other multimodal regimens. These findings support the use of opioid-sparing multimodal analgesia into postoperative care to reduce O-PONV in this surgical population.

Abbreviations

NMA
Network meta-analysis
NSAIDs
Nonsteroidal anti-inflammatory drugs
O-PONV
Opioid-associated postoperative nausea and vomiting
PONV
Postoperative nausea and vomiting
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT
Randomized controlled trial
RoB2
Risk of Bias 2

Declarations

Clinical trial number: not applicable.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Author Contribution

SC and SS led the study design, data extraction, statistical analysis, interpretation of the results, and manuscript drafting. SC and JK conducted the literature search and study selection. SC, SS, and KB conducted the risk of bias assessment. PL and EL contributed to the conception of the research, provided oversight and feedback throughout the study, and critically reviewed the manuscript. All authors contributed to writing and revising the manuscript, agreed the final version.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary information files.

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Figures

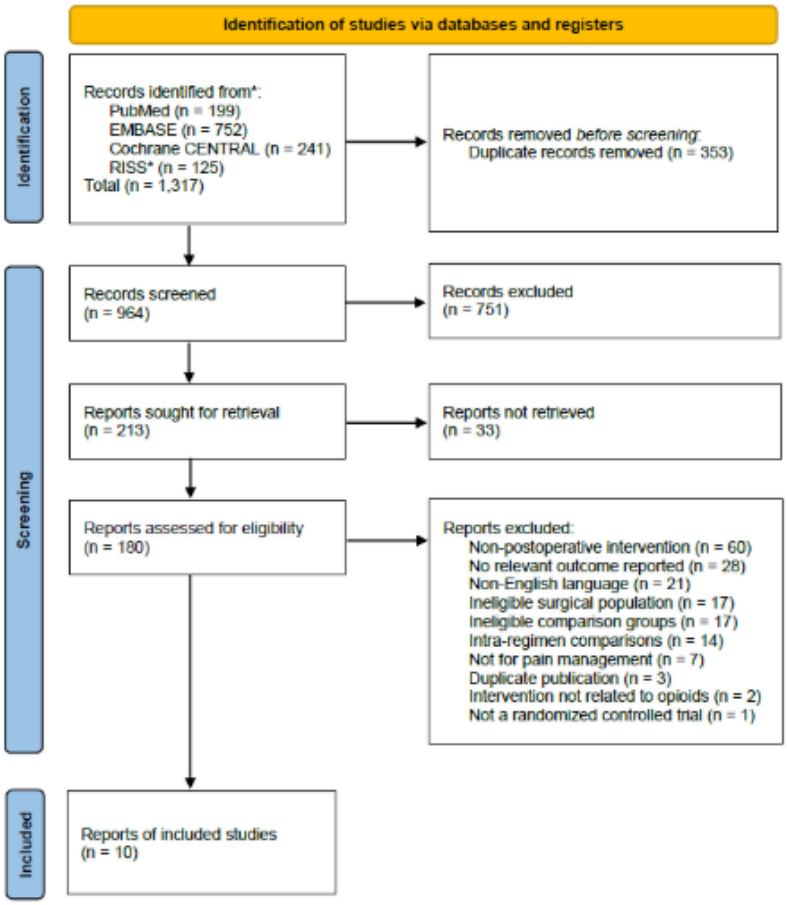


Figure 1

PRISMA flow diagram of study screening. *RISS: Research Information Sharing Service database operated by the Korea Education & Research Information Service.

	D1	D2	D3	D4	D5	Overall
Blackburn et. al, 1995	+	+	+	+	+	+
Castro-Alves et. al, 2016	+	+	+	+	!	!
Cobby et. al, 1999	+	+	+	+	+	+
Dierking et. al, 2004	+	+	+	+	!	!
Gunusen et. al, 2004	+	+	+	+	+	+
Hercock et. al, 1999	+	+	+	+	+	+
Jarruwale et. al, 2016	+	+	+	+	+	+
Lin T. F. et. al, 2009	+	+	+	+	+	+
Ng A. et. al, 2002	!	+	+	+	+	!
Yucel et. al, 2011	+	+	+	+	+	+

+ Low risk
! Some concerns
- High risk

D1 Randomization process
D2 Deviations from the intended interventions
D3 Missing outcome data
D4 Measurement of the outcome
D5 Selection of the reported result

Figure 2

Summary of risk of bias assessment

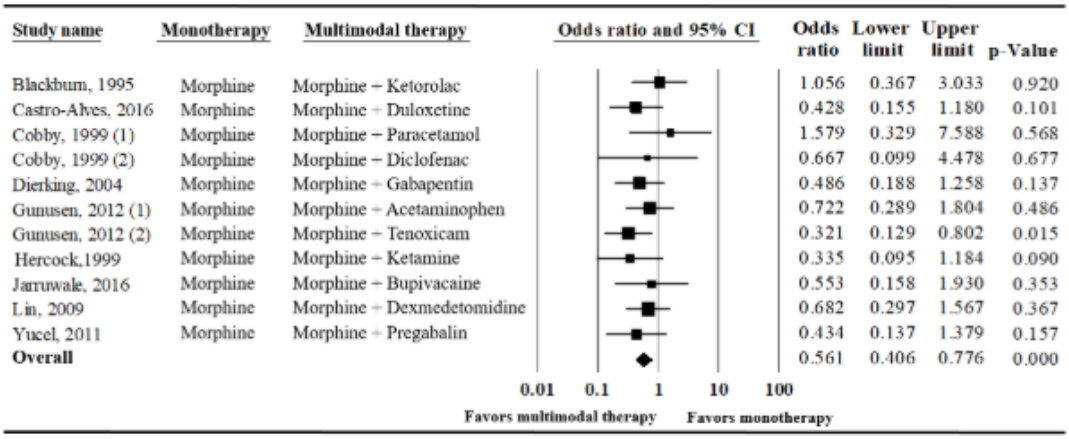


Figure 3

Forest plot of postoperative nausea or vomiting incidence comparing morphine monotherapy and multimodal therapy

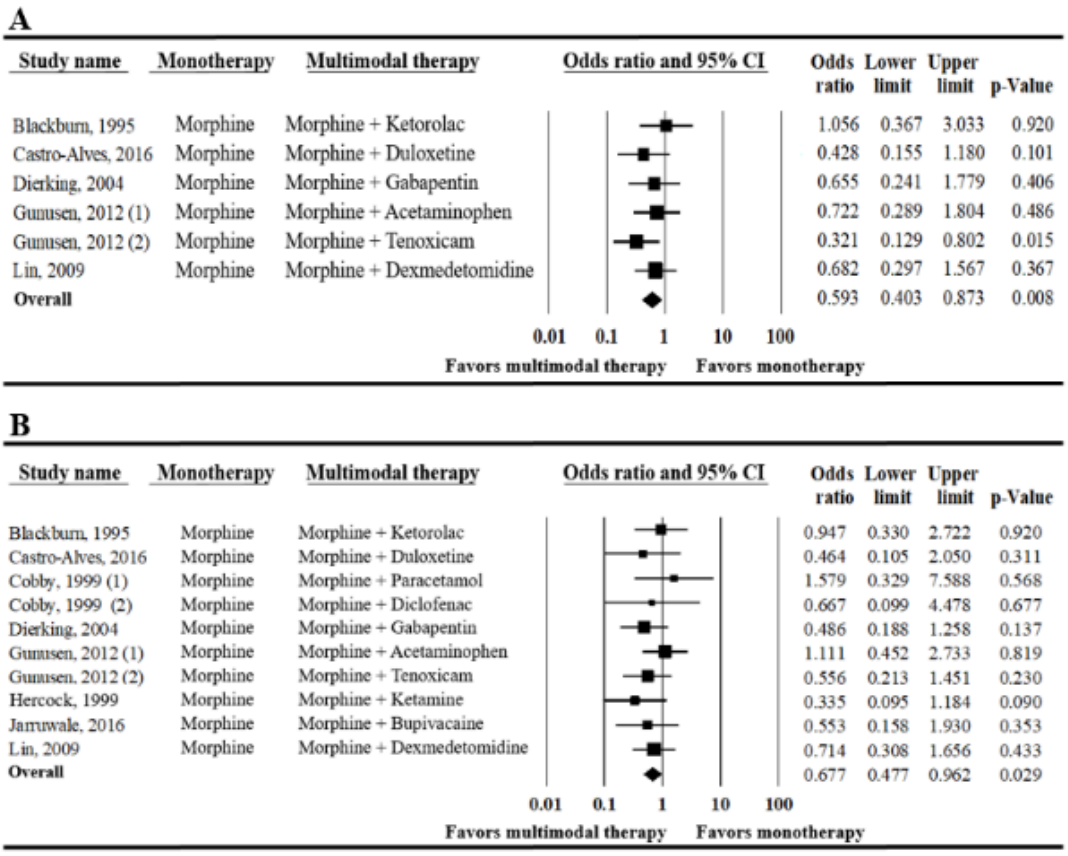


Figure 4

Forest plots of postoperative nausea incidence (A) and vomiting incidence (B) comparing morphine monotherapy and multimodal therapy

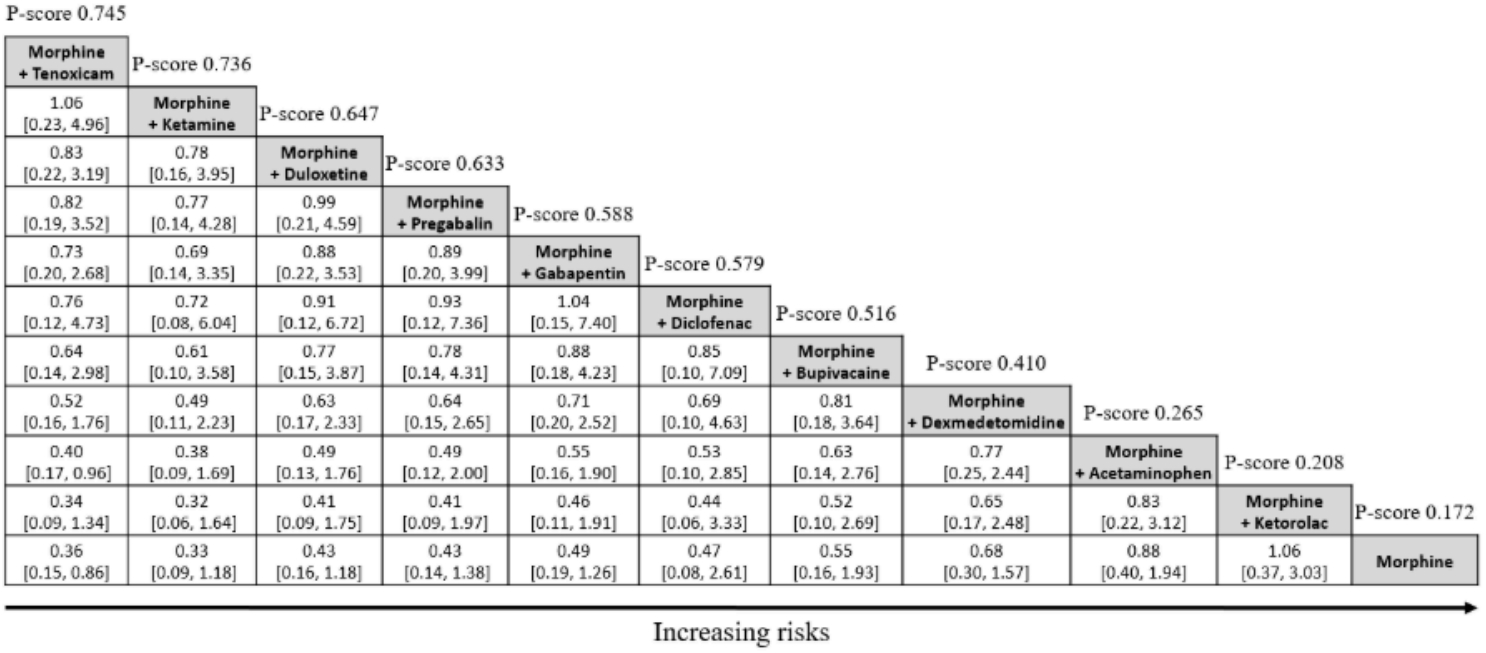


Figure 5

League table of network meta-analysis ranked by P-score

Supplementary Files

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- OpioidAbdSupplementary261007.docx