Perioperative Multimodal Analgesia for Adults Undergoing Surgery of the Spine—A Systematic Review and Meta-Analysis of Three or More Modalities

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Key words
- Multimodal analgesia
- Perioperative outcomes
- Spinal surgery

Abbreviations and Acronyms
CI: Confidence interval
GRADE: Grading of recommendations, assessment, development, and evaluation
MD: Mean difference
PRISMA: Preferred reporting items for systematic reviews and meta-analysis
SMD: Standardized mean difference
VAS: Visual analog scale

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BACKGROUND: **Multimodal analgesia is a strategy that can be used to improve pain management in the perioperative period for patients undergoing surgery of the spine. However, no review evidence is available on the quantitative models of multimodal analgesia within this clinical setting. We conducted a systematic review and meta-analysis to examine the effects of maximal (≥3 analgesic agents) multimodal analgesic medication for patients undergoing surgery of the spine.**

METHODS: **We included randomized controlled trials that had evaluated the use of ≥3 multimodal analgesia components (maximal multimodal analgesia) in patients undergoing spinal surgery. We excluded patients who had received neuraxial or regional analgesia. The control group consisted of placebo, standard care (any therapeutic modality including ≤2 analgesic components). The primary outcomes were the postoperative pain scores at rest evaluated at 24 and 48 hours. We searched MEDLINE via OvidSP, EMBASE via OvidSP, and the Cochrane Library (Cochrane Database of Systematic Reviews and CENTRAL). We used the Cochrane standard methods.**

RESULTS: **We identified consistently improved analgesic endpoints across all predetermined primary and secondary outcomes. A total of 11 eligible studies had evaluated the primary outcome of pain at rest at 24 hours. The patients who had received maximal multimodal analgesia were identified to have had lower pain scores with an average mean difference of −1.03 ($P < 0.00001$). The length of hospital stay was shorter for the patients who had received multimodal analgesia (mean difference, −0.55; $P < 0.00001$).**

CONCLUSIONS: **Perioperative maximal multimodal analgesia consistently improved the visual analog scale scores for an adult population in the immediate postoperative period, with a moderate quality of evidence. We found a significant decrease in the hospital length of stay for patients who had received maximal multimodal analgesia with a high level of evidence and no statistical heterogeneity.**

INTRODUCTION

Spinal surgeries have traditionally been associated with high perioperative pain scores, significant opioid requirements, and delayed functional recovery.[1] Poorly controlled pain after spine surgery can decrease mobility and affect patient recovery. These can result in increased rates of complications, including deep venous thrombosis, pulmonary embolism, and pneumonia.[1] Effective pain control can improve the quality of recovery scores, postoperative rehabilitation, and long-term surgical outcomes.[2] Opioid analgesics have been a common choice for the management of perioperative pain. However, opioids are associated with a number of side effects, including increased sedation, somnolence, and pruritus and an increased risk of nausea and vomiting and respiratory depression.[3]

Prior investigations have demonstrated that postoperative pain after spine surgery can involve multiple pathways, including neuropathic, inflammatory, and nociceptive pain responses.[4] There is a complement of nonopioid therapeutic strategies available. The findings from 2 prior meta-analyses have supported the use of nonsteroidal anti-inflammatory drugs.[5,6] A meta-analysis of 14 trials found that supplemental perioperative ketamine reduced postoperative opioid consumption for ≤24 hours after spine surgery.[7] Individual studies have demonstrated the opioid-sparing effects of methadone when used for patients undergoing surgery of the spine.[8] A recent meta-analysis demonstrated that perioperative intravenous lidocaine infusion consistently improved the analgesic outcomes in the first 24 hours postoperatively for patients who had undergone surgery of the spine.[9]

Multimodal analgesia can be defined as systemic administration of ≥2 drugs or the combination of ≥2 pain management modalities (e.g., regional anesthesia techniques such as central neuraxial and

Table 1. PICO Review Approach Illustrating Eligibility Criteria (Patient Population, Intervention and Comparator) and Listed Outcomes

Study Characteristic	Inclusion Criteria	Exclusion Criteria
Patient population	All adult patients who had undergone spinal surgical procedures	Patients who had undergone nonoperative management of spinal conditions; pediatric patients who had undergone spinal surgery
Intervention or treatment	Three or more multimodal analgesic components, including combinations of paracetamol, NSAIDs, COX inhibitors, NMDA antagonists, α_2-blocking agents, magnesium, IV lidocaine, local anesthetic infiltrative techniques, and opioids	Regional anesthetic techniques and neuraxial analgesia
Comparator	Placebo or standard of care (any therapeutic modality, including ≤2 multimodal components)	NA
Outcomes	Primary outcome measure: pain score at rest at 24 and 48 hours; secondary outcome measures: postoperative opioid consumption at 24 and 48 hours postoperatively; hospital length of stay (measured in days); postoperative nausea and vomiting in 24-hour postoperative period; adverse respiratory events in 24-hour postoperative period	NA

PICO, population, intervention, comparison, and outcomes; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase; NMDA, N-methyl-D-aspartate; IV, intravenous; NA, not applicable.

peripheral nerve blocks) with different mechanisms of action to provide analgesia by targeting different parts of the body that modulate pain. It is thought that multimodal analgesic components act synergistically on different pathways of nociception to provide pain relief and minimize side effects. Level 3 evidence from cohort studies has shown that stepwise improvements in analgesia can be achieved through greater multimodal contributions.[10] Prior systematic reviews and recently published guidelines have provided a narrative synopsis on the individual multimodal analgesic options available for surgery of the spine.[1,2,11,12] Therefore, the literature has been adequately addressed by several reports of detailed analyses of individual treatment concepts. However, analyses of the efficacy of maximal multimodal analgesia (i.e., the utility of ≥3 agents in the provision of analgesia) in the perioperative period for patients undergoing spinal surgery have been limited.

Quantitative evaluations of the effectiveness of a combination of multimodal analgesic options to provide level 1 practice evidence for use in clinical practice have been limited. To the best of our knowledge, the present study is the first systematic review and quantitative analysis of maximal (≥3) analgesic modalities after surgery of the spine. We hypothesized that any maximal combination using ≥3 modalities of accepted practice of multimodal analgesic regimens would achieve efficacy for patients undergoing surgery of the spine. We focused on any combination of ≥3 intravenously administered agents to explore the synergism of the effect. The interventions studied were diverse and had been administered in accordance with the individual study design. Our goal was to explore the efficacy of a generous multimodal approach in terms of the number of interventions (≥3) rather than the specific pharmacodynamic interactions. Thus, we did not focus on specific drug pharmacodynamics but rather the compound effect of the maximal multimodal analgesic therapy on predetermined outcomes. We estimated that this would reflect current clinical practice in which institutions might choose to use specific multimodal regimens.

We hypothesized that the synergism of the multiple, appropriately administered, analgesics would provide additional benefit. In the present systematic review, we assessed the analgesic effects of maximal (≥3 multimodal analgesic components) compared with placebo or alternative treatment on postoperative pain and recovery for patients who had undergone spinal surgical procedures. This quantitative pharmacodynamic model has been frequently used in clinical practice but has not been explored through a formal systematic review and meta-analysis.

METHODS

Protocol and Registration

We performed and reported the present systematic review and meta-analysis using the recommended Cochrane methods and standards.[13] We used the PRISMA (preferred reporting items for systematic reviews and meta-analyses) statement to report our findings (**Supplementary Table 1**).[14] We prospectively registered the protocol for our review within the PROSPERO (International Prospective Register of Systematic Reviews; systematic review registration identification no. CRD42021258554; available at: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=258554). Formal ethical approval was not required because primary patient data were not collected.

Eligibility Criteria

The eligibility criteria for the present review have been described according to the patient population, intervention, and comparator parameters. All adult patients who had undergone spinal surgical procedures were eligible. Patients who had received nonoperative management of spinal conditions were excluded. Pediatric patients who had undergone surgery of the spine were also excluded. To be eligible, the studies were required to have used ≥3 multimodal analgesic components, including a combination of paracetamol, nonsteroidal anti-inflammatory drugs, cyclooxygenase inhibitors, N-methyl-D-aspartate antagonists, α_2-blocking agents, magnesium, intravenous lidocaine, local anesthetic

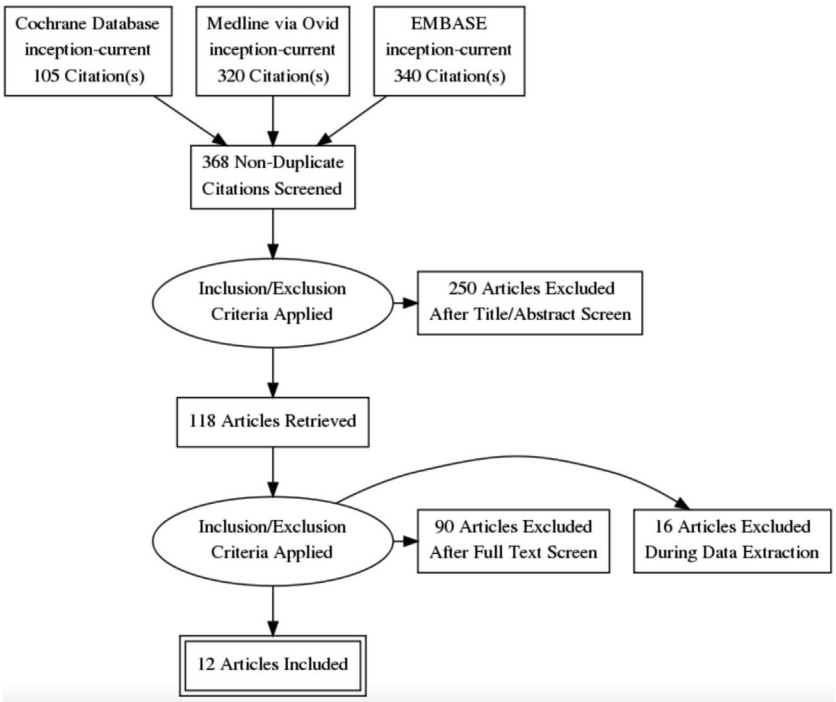


Figure 1. We used the visual analog scale (VAS; 0–10 cm or 0–100 mm) to report the outcomes. If data had been presented using a numerical rating scale (0–10 cm or 0–100 mm), we converted to the data to the VAS. We used intravenous morphine equivalents to report postoperative opioid consumption. The data were insufficient to conduct a preplanned meta-analysis for a number of outcomes, including pain with movement at 24 and 48 hours and the quality of recovery outcomes on days 2, 3, and 4. The included trials had only reported those adverse postoperative events that had occurred rather than other anticipated adverse outcomes. As such, the adverse events composite outcome consisted of adverse respiratory events. Because many of the included studies had reported 12-hour VAS scores for pain, we performed a post hoc analysis of the data to explore the heterogeneity identified in the primary outcomes.

infiltrative techniques, and opioids. The present review was of maximal (>3) multimodal analgesia; thus, randomized controlled trials that had studied the effects of a combination of ≥3 multimodal analgesics were included. Multimodal analgesics could have been administered orally or intravenously. We also included studies that had used local infiltration. We included studies that had incorporated preoperative multimodal analgesia with the requirement that multimodal analgesia had been continued postoperatively. Standard treatment was defined as any analgesic modality that had used a placebo or <3 analgesic options. We excluded studies that had used regional analgesia (e.g., erector spinae blocks). We also excluded studies that had compared intrathecal or epidural analgesia against standard therapy. We excluded these studies owing to the potential for out-of-scope clinical diversity. We included adult population studies reported in the English language. The PICOS (population, intervention, comparison, outcomes, study design) review approach, with the patient population, intervention, and comparator as eligibility criteria and the listed outcomes, is presented in **Table 1**.

Information Sources and Search Strategy

The following electronic databases were searched: MEDLINE via OvidSP, EMBASE via OvidSP, and Cochrane Library, including the Cochrane Database of Systematic Reviews. We scanned ClinicalTrials.gov for current trials. Gray literature was searched using specific search engines (Google scholar; http://www.opengrey.eu; and http://www.greynet.org/opengreyrepository.html).[15-17] We used keywords and search strategies tailored to the individual databases. The specific search strategy for MEDLINE via OvidSP is presented in the **Supplementary Methods**.

Data Management

EndNote X9 (Clarivate, London, UK) was used to record and organize the pertinent study data extracted. Both of us (L.S., A.S.) separately reviewed the study titles and abstracts using an electronic platform (Covidence web platform; available at: http://www.COVIDENCE.org). Studies were deemed suitable if both reviewers agreed on study inclusion. Disagreements were resolved through discussion. The results of the study search and management are presented as a PRISMA flow diagram in **Figure 1**. One of us extracted the relevant data, and the other checked the data accuracy. We contacted the authors of the primary reports if data were missing or needed to be clarified.

Outcomes and Prioritization

The primary outcomes were as follows:

1. Pain score at rest measured at 24 hours postoperatively
2. Pain score at rest measured at 48 hours postoperatively

The secondary outcomes were as follows:

1. Postoperative opioid consumption 24 and 48 hours postoperatively
2. Hospital length of stay measured in days
3. Postoperative nausea and vomiting in the 24-hour postoperative period
4. Composite morbidity consisting of adverse respiratory events during hospital admission (no other adverse outcomes were reported)

Data Synthesis

We used clinical judgment to assess whether the studies were sufficiently homogeneous enough to combine the data. For the studies to be considered similar enough, we reviewed the patient populations studied and patterns of analgesic administration. We determined statistical heterogeneity using the χ^2 test and I^2

Table 2. Spinal Surgery Groups

Major surgery
Anterior cervical decompression and fusion
Posterior cervical decompression/fusion
Thoracic decompression and fusion
Scoliosis correction
Multilevel decompression and fusion
Lumbar decompression and fusion
Minor surgery
Lumbar laminectomy
Lumbar microdiscectomy

statistic. We considered a high χ^2 value or low P value as statistical evidence of the heterogeneity of intervention effects. We interpreted the I^2 statistic in the context of 1) the magnitude and direction of the effects and 2) the strength of the evidence for heterogeneity.[13] Absolute statistical values for heterogeneity were interpreted in line with the reported Cochrane method: 1) not important, an I^2 of 0%–40%; 2) moderate, an I^2 of 30%–60%; 3) substantial, an I^2 of 50%–90%; and 4) considerable, an I^2 of 75%–100%.[13] We used RevMan, version 5.3, software (Cochrane Training, London, UK) for data synthesis and meta-analysis. We used the random effects model in the meta-analysis to adjust the study weights according to the heterogeneity among the interventions. Continuous outcomes were analyzed using an inverse variance weighting summary. A few events were found in the dichotomous data (adverse events). Therefore, we used the Mantel-Haenszel method for dichotomous outcomes.[18] Some studies had presented their data as the median and interquartile range. When the data had been presented in this format, we transformed the data using acceptable methods for our review.[19]

Measures of Treatment Effect

Dichotomous outcomes were calculated in the format of risk ratios between the intervention group and control group event rates. For the continuous outcomes, we calculated the mean difference (MD) and standard deviation if the studies had used the same scale to measure the outcomes. We used the standardized mean difference (SMD) when the outcomes in the studies had been reported using different scales. The intravenous morphine equivalents measurement scale was used to analyze the opioid quantities in accordance with the defined daily dose index[20] and opioid dose equivalence reported by the Faculty of Pain Medicine, Australian and New Zealand College of Anaesthetists.

Risk of Bias in Individual Studies

We used the Cochrane risk of bias tool to assess the risk of bias in the individual studies.[21,22] The updated tool uses 6 key parameters: 1) random sequence generation; 2) allocation concealment; 3) blinding of participants, personnel, and outcome assessors; 4) incomplete outcome data; 5) selective reporting; and 6) any other bias. We generated a risk of bias and a risk of bias summary.[23]

Confidence in Cumulative Evidence

In addition to assessing the risk of bias in the individual studies, we classified the quality of the body of evidence across the individual outcomes using the GRADE (grading of recommendations, assessment, development, and evaluation) framework.[24-26] We used GRADEpro software to generate evidence profile and summary of findings tables.[21,27] We used the GRADE framework to appraise the extent to which one could be confident that the estimates of effect reflected the item assessed. The quality of the body of evidence reflects the within-study risk of bias (methodological quality), indirectness, data heterogeneity (inconsistency), imprecision of effect estimates, and risk of publication bias.[9,27]

Subgroup Analysis

A subgroup analysis, as planned in the protocol, was performed to review the subgroup of major surgery patients when minor surgery patients were excluded. We defined minor surgery as patients who had undergone lumbar laminectomy or microdiscectomy (**Table 2**). To explore sources of heterogeneity, we performed 2 additional subgroup analyses. We analyzed patients for whom α_2-agonists had been used as a part of the analgesic regimen compared with standard treatment. We performed a subgroup analysis of patients for whom ketamine had been used as a part of the analgesic regimen.

Meta-Biases

We searched for registered and/or published study protocols. Publication bias was addressed by searching for published protocols of the included studies. We assessed for selective outcome reporting by comparing the reported studies with the planned protocols. We constructed the funnel plots for the studies reporting primary outcomes. We visually examined the effect estimates using the funnel plot for signs of asymmetry. In addition, we performed a quantitative statistical analysis (Egger's test) to formally assess the funnel plot asymmetry.[28] We used Stata, version 16 (StataCorp, College Station, Texas, USA), to quantitatively examine the results using the Egger regression-based meta-bias test.

RESULTS

Search Results

The results of the literature search are presented graphically in **Figure 1**.

Study Selection and Characteristics

We identified a total of 12 studies eligible for inclusion in our review (**Table 3**; **Supplementary Table 2**). We included randomized controlled studies that had compared the use of $\geq$3 multimodal analgesia components. The individual study characteristics are listed in **Supplementary Table 2**. All the studies had used $\geq$3 multimodal analgesics in the perioperative period. Multimodal analgesia had either been started preemptively or intraoperatively and continued in the postoperative period.

Primary Outcome

Our primary aim was to examine the effects of quantitative pharmacodynamic modeling rather than the qualitative action of the individual analgesic therapy. The identified studies appeared clinically homogeneous owing to consistent analgesic use and the proven efficacy of the dosages and timing used. We considered that the

Table 3. Analgesic Modalities Used by Included Studies

Investigator	Modality									Surgery Group
	PO/IV Paracetamol	NSAIDs COX	Pregabalin/ Gabapentin	IV Ketamine; IV Methadone	IV Lidocaine	IV Dexmedetomidine or Clonidine	Local Infiltration	Other*	Opioids	
Garcia et al.,[29] 2013	−	−	+	−	−	−	−	−	+	Minor
Govil et al.,[30] 2020	+	−	−	−	−	−	−	+	+	Major
Ibrahim et al.,[31] 2018	+	+	−	−	+	−	−	−	+	Major
Kim et al.,[32] 2016	+	−	+	−	−	−	−	−	+	Major
Liu et al.,[33] 2020	−	−	−	−	−	−	+	+	+	Major
Maheshwari et al.,[34] 2020	−	−	+	+	+	−	+	−	+	Major
Murphy et al.,[8] 2021	−	−	−	++	−	−	−	−	+	Major
Nitta et al.,[35] 2013	−	−	−	+	−	+	−	+	+	Major
Pacreu et al.,[36] 2012	+	+	−	++	−	−	−	−	+	Both
Raja et al.,[37] 2019	+	+	−	−	−	−	−	+	+	Both
Soffin et al.,[38] 2020	−	+	−	+	+	−	−	−	+	Major
Zhang et al.,[39] 2021	+	+	+	−	−	−	−	−	+	Major

PO, oral; IV, intravenous; NSAIDs, nonsteroidal anti-inflammatory drugs; COX, cyclooxygenase (inhibitor).
*Duloxetine and/or tramadol hydrochloride.

use of different modalities would closely represent the real-world situation of the patterns of analgesia use. We, therefore, assessed the clinical homogeneity of the studies as suitable for the meta-analysis. All the pain score results in the studies had been reported using the visual analog scale (VAS). We recorded the MD at 12, 24, and 48 hours postoperatively (Figure 2) because all the studies had also used the VAS to measure the analgesic effects. Multimodal analgesic combinations of ≥3 different agents had decreased the recorded pain scores at 24 hours (MD, −1.03 [95% confidence interval (CI), −1.42 to −0.64]; $P < 0.00001$and 48 hours (MD, −1.16 [95% CI, −1.56 to −0.76]; $P < 0.00001$) postoperatively in the experimental group compared with those in the control group.

Statistical heterogeneity was identified across the primary outcomes. We noted considerable statistical heterogeneity at 24 and 48 hours.[13] We constructed a funnel plot graph to explore the effects of small studies (Figure 3). However, smaller studies did not demonstrate a larger effect. The P values for the Egger test did not reach statistical significance at 24 hours ($P < 0.45$; Egger's test performed using Stata, version 16 [StataCorp]).

To explore the causes of heterogeneity, we performed a post hoc analysis of the VAS scores at 12 hours. Four studies had reported on this outcome. We found a significant decrease in pain scores for the patients who had received quantitative multimodal analgesia (MD, −2.15 [95% CI, −2.61 to −1.68]; $P < 0.001$) with moderate heterogeneity.

Secondary Outcomes

Postoperative opioid consumption had decreased in the 24-hour period after surgery (SMD, −0.91 [95% CI, −1.09 to 0.73]; $P < 0.000001$). We noted substantial statistical heterogeneity for this outcome. Four studies had reported opioid consumption in the 48-hour period (SMD, −1.16 [95% CI, −1.56 to −0.76]). Substantial statistical heterogeneity remained (Figure 4).

The hospital length of stay, measured in days, was significantly shorter for the group that had received multimodal analgesia (MD, −0.55 [95% CI, −0.81 to −0.3]; $P < 0.0001$; Figure 5). We identified no meaningful heterogeneity

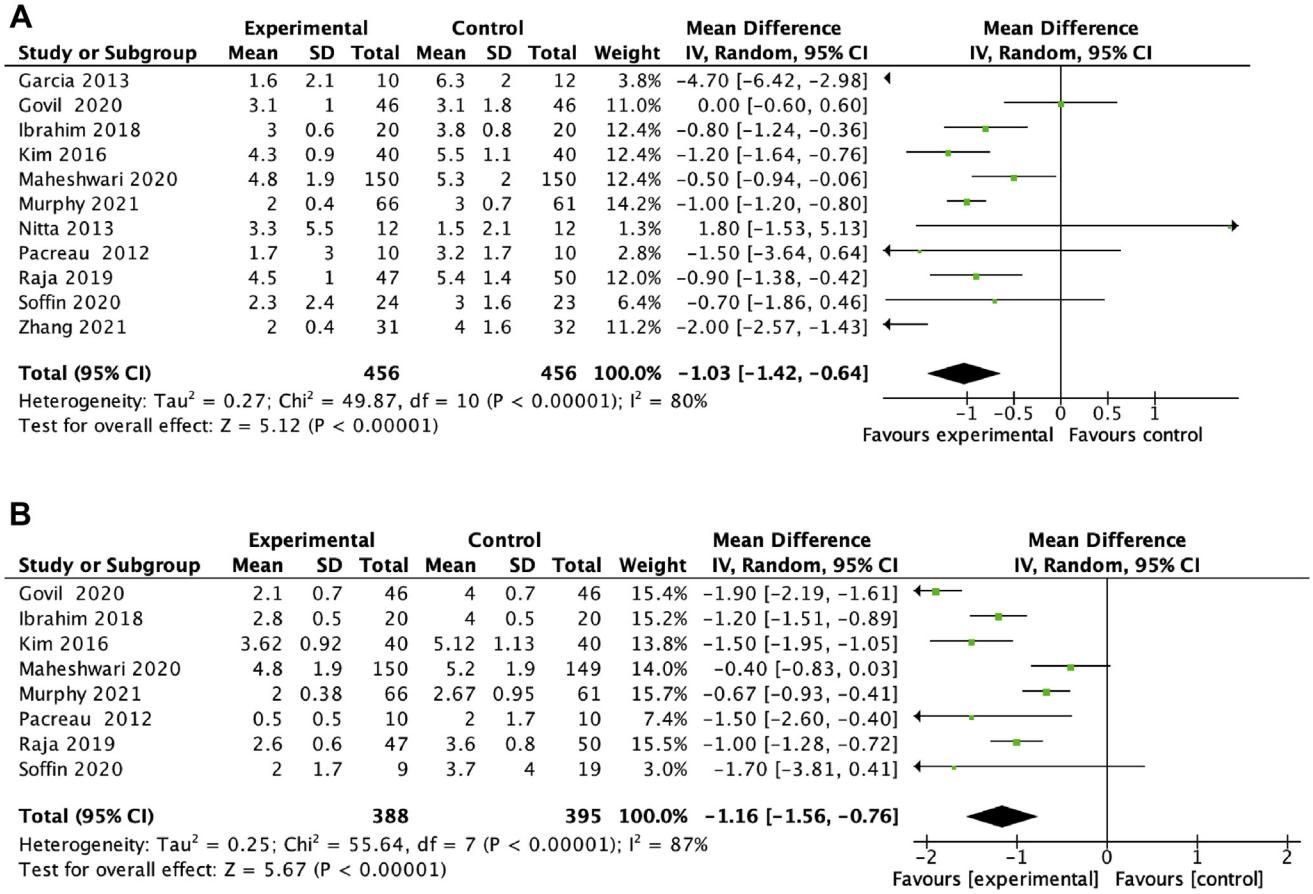


Figure 2. (**A, B**) Forest plots showing the VAS mean difference at 24 and 48 hours. CI, confidence interval; SD, standard deviation.

for this outcome. We found no notable differences between the intervention and standard groups regarding the incidence of postoperative nausea and vomiting in the first 24 hours (MD, 0.79 [95% CI, 0.57−1.10]; P = 0.17) or adverse respiratory events during admission (Supplementary Figure 1).

Sensitivity Analysis

We performed a sensitivity analysis across the primary outcomes. We excluded studies with a high risk of bias (≥1 fields with a high risk of bias). The robustness of summary statistics was maintained across the measured VAS scores at 24 hours (MD, −0.70 [95% CI, −1.00 to −0.41]) and 48 hours (MD, −1.07 [95% CI, −1.54 to −0.60]; P < 0.00001). Heterogeneity was significantly lower at 24 hours when the studies with a high risk of bias had been excluded (I^2, 52%; moderate; Figure 6).

Subgroup Analysis

A comparison of major versus minor surgery was not performed because most of the studies had included minor surgery had also included patients who had required major surgery. We conducted an analysis of the efficacy of multimodal analgesia for patients undergoing major surgery. To explore the causes of heterogeneity, we conducted a subgroup analysis of the primary outcomes for the patients after excluding the patients who had received α_2-agonists and of a subgroup of patients who had not received ketamine. The efficacy of multimodal analgesia was maintained for the patients who had required major surgery (Figure 7). The efficacy of the multimodal analgesia was also maintained for the patients who had not received clonidine and those who not received ketamine, with no changes in the heterogeneity parameters.

Risk of Bias of Included Studies

A risk of bias graph and summary are presented in Figure 8. All the bias measurement parameters demonstrated a low risk of bias in >50% of the included studies (Supplementary Table 3). The use of blinding of the participants was difficult or unclear in 4 of the studies.[29,32,33,35]

Confidence in Cumulative Evidence: Summary of Findings and GRADE

We used the GRADE classification system to assess the quality of the body of evidence across the primary and secondary outcomes. The imprecision criterion was downgraded owing to the variability of the effect. We downgraded the inconsistency

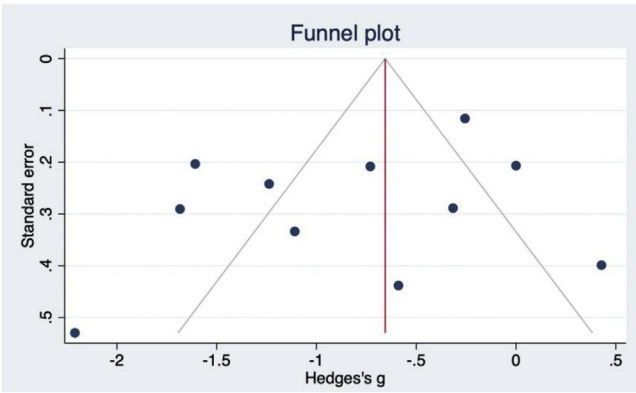


Figure 3. Funnel plot showing small study effects.

criterion when the heterogeneity was substantial. Despite downgrading the inconsistency criterion as a measure of heterogeneity, we identified a moderate level of evidence for the use of multimodal analgesia to improve the outcomes across most of the primary outcomes studied (Supplementary Tables 4 and 5). With low heterogeneity and, therefore, low inconsistency, a high level of evidence was identified for quantitative maximal analgesic modeling to decrease the hospital length of stay.

Meta-Biases

We addressed the publication bias by searching for the published protocols of the relevant studies. We did not identify selective reporting across the studies. When performing the Egger test, we did not visually identify asymmetry of the funnel plot.[28] We identified a low likelihood of a meta-bias according to the statistical testing results ($P < 0.45$).

DISCUSSION

We found a high quality of evidence for the efficacy of maximal quantitative multimodal analgesia to decrease the hospital length of stay, with low statistical heterogeneity. Perioperative analgesia with ≥3 modalities consistently improved the VAS scores for the adult population at 24 hours after surgery. Improvement in the VAS scores at 24 hours was consistently associated with a decrease in the VAS scores at 12 and 48 hours. The statistical heterogeneity was low for the primary outcome of the VAS score at 24 hours once the studies with a high risk of bias had been excluded. This improvement in the VAS outcomes was supported by a moderate level of evidence. We found a demonstrated

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Garcia 2013	20.3	12.1	10	42.2	19.4	12	3.8%	−1.28 [−2.21, −0.34]
Govil 2020	10.43	1.51	46	12.55	1.74	46	16.5%	−1.29 [−1.74, −0.84]
Ibrahim 2018	5.4	4.5	20	19.9	9	20	5.6%	−2.00 [−2.77, −1.22]
Maheshwari 2020	35.3	15.7	150	39.75	18	149	64.9%	−0.26 [−0.49, −0.04]
Murphy 2021	22.5	11.7	66	70	12	61	9.1%	−3.99 [−4.59, −3.38]
Total (95% CI)			**292**			**288**	**100.0%**	**−0.91 [−1.09, −0.73]**

Heterogeneity: $Chi^2 = 140.42$, df = 4 ($P < 0.00001$); $I^2 = 97\%$
Test for overall effect: $Z = 9.71$ ($P < 0.00001$)

Std. Mean Difference IV, Fixed, 95% CI
−1 −0.5 0 0.5 1
Favours [experimental] Favours [control]

B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Govil 2020	2.1	0.7	46	4	0.7	46	15.4%	−1.90 [−2.19, −1.61]
Ibrahim 2018	2.8	0.5	20	4	0.5	20	15.2%	−1.20 [−1.51, −0.89]
Kim 2016	3.62	0.92	40	5.12	1.13	40	13.8%	−1.50 [−1.95, −1.05]
Maheshwari 2020	4.8	1.9	150	5.2	1.9	149	14.0%	−0.40 [−0.83, 0.03]
Murphy 2021	2	0.38	66	2.67	0.95	61	15.7%	−0.67 [−0.93, −0.41]
Pacreau 2012	0.5	0.5	10	2	1.7	10	7.4%	−1.50 [−2.60, −0.40]
Raja 2019	2.6	0.6	47	3.6	0.8	50	15.5%	−1.00 [−1.28, −0.72]
Soffin 2020	2	1.7	9	3.7	4	19	3.0%	−1.70 [−3.81, 0.41]
Total (95% CI)			**388**			**395**	**100.0%**	**−1.16 [−1.56, −0.76]**

Heterogeneity: $Tau^2 = 0.25$; $Chi^2 = 55.64$, df = 7 ($P < 0.00001$); $I^2 = 87\%$
Test for overall effect: $Z = 5.67$ ($P < 0.00001$)

Mean Difference IV, Random, 95% CI
−2 −1 0 1 2
Favours [experimental] Favours [control]

Figure 4. (**A, B**) Forest plots showing opioid consumption. CI, confidence interval; SD, standard deviation.

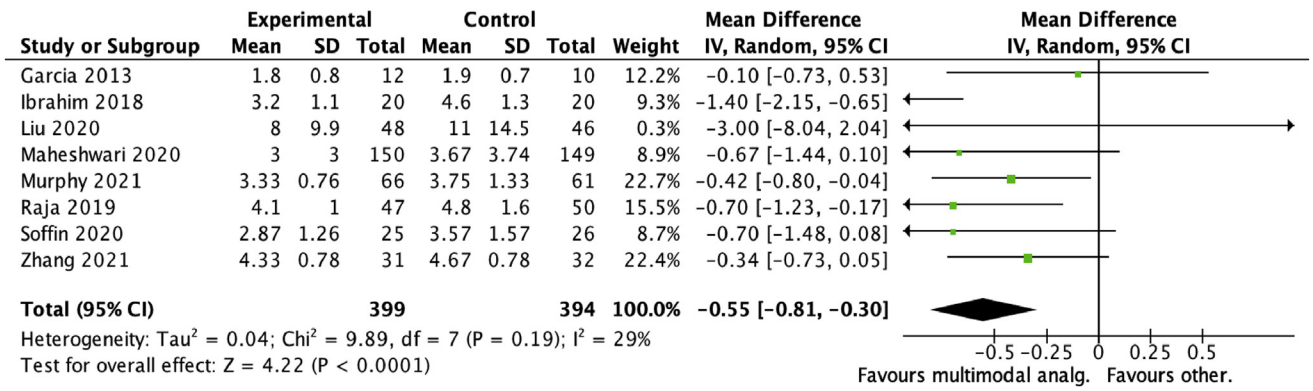


Figure 5. Forest plots showing hospital length of stay. CI, confidence interval; SD, standard deviation.

decrease in opioid consumption at 24 and 48 hours postoperatively in the adult population, albeit of low magnitude. The improvements in analgesic outcomes were not reflected by the frequency of adverse outcomes.

The average pain reduction in the 24-hour postoperative period was a MD of −1.03, with greater effects seen at 12 and 48 hours. The quality evidence was moderate for the intervention. A study measuring the minimal clinically important difference in acute pain for patients identified a change of 10 on a 100-mm VAS for pain, signifying a clinically important improvement or deterioration.[40] Other systematic reviews of acute pain measurements have indicated the

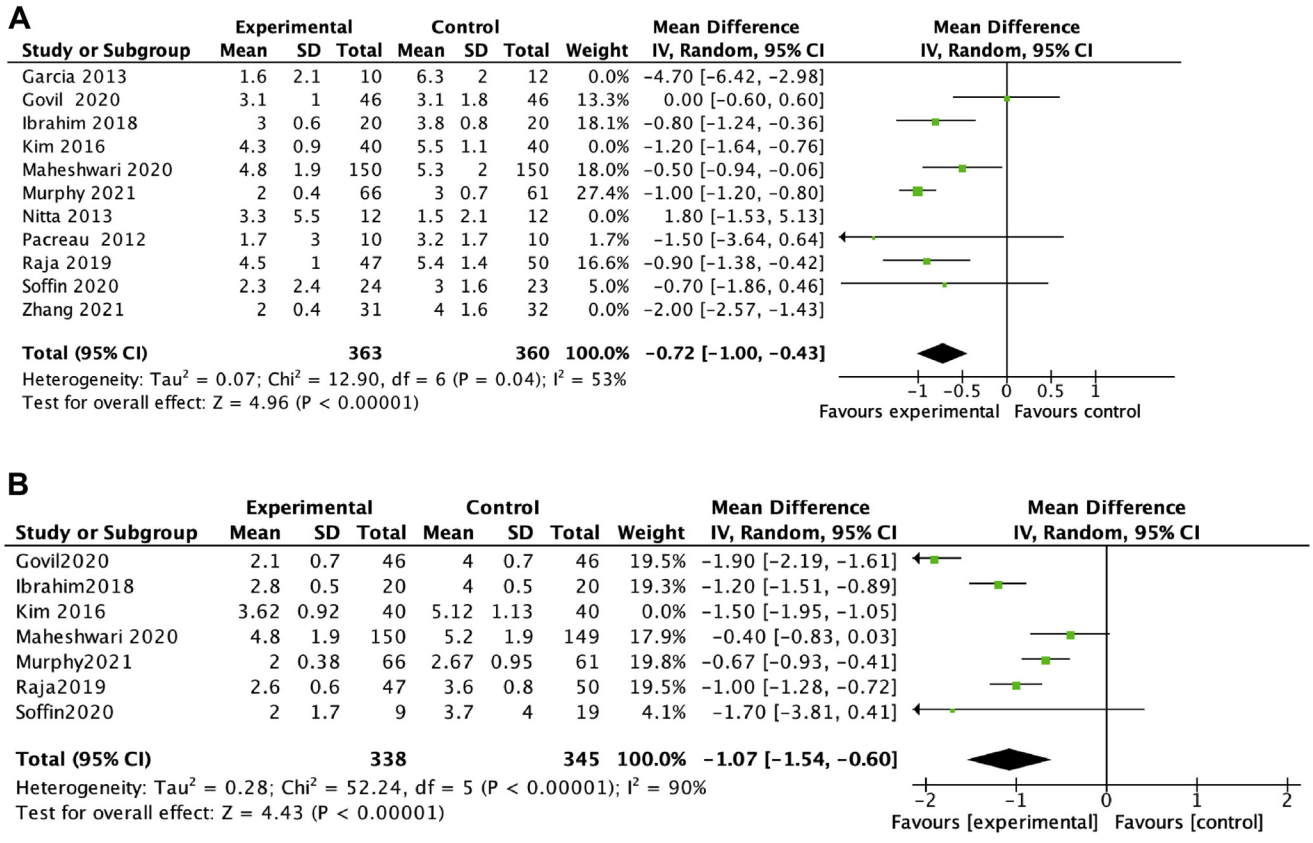
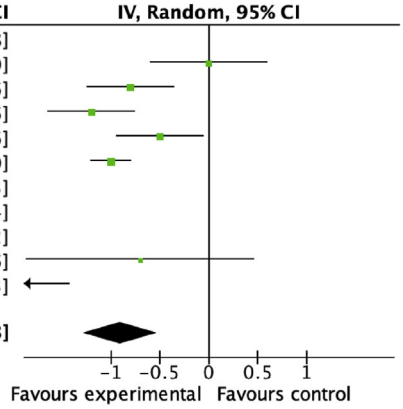


Figure 6. Forest plots demonstrating sensitivity analysis.

A

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Garcia 2013	1.6	2.1	10	6.3	2	12	0.0%	−4.70 [−6.42, −2.98]
Govil 2020	3.1	1	46	3.1	1.8	46	13.4%	0.00 [−0.60, 0.60]
Ibrahim 2018	3	0.6	20	3.8	0.8	20	15.7%	−0.80 [−1.24, −0.36]
Kim 2016	4.3	0.9	40	5.5	1.1	40	15.7%	−1.20 [−1.64, −0.76]
Maheshwari 2020	4.8	1.9	150	5.3	2	150	15.7%	−0.50 [−0.94, −0.06]
Murphy 2021	2	0.4	66	3	0.7	61	18.9%	−1.00 [−1.20, −0.80]
Nitta 2013	3.3	5.5	12	1.5	2.1	12	0.0%	1.80 [−1.53, 5.13]
Pacreau 2012	1.7	3	10	3.2	1.7	10	0.0%	−1.50 [−3.64, 0.64]
Raja 2019	4.5	1	47	5.4	1.4	50	0.0%	−0.90 [−1.38, −0.42]
Soffin 2020	2.3	2.4	24	3	1.6	23	6.9%	−0.70 [−1.86, 0.46]
Zhang 2021	2	0.4	31	4	1.6	32	13.7%	−2.00 [−2.57, −1.43]
Total (95% CI)			**377**			**372**	**100.0%**	**−0.90 [−1.28, −0.53]**

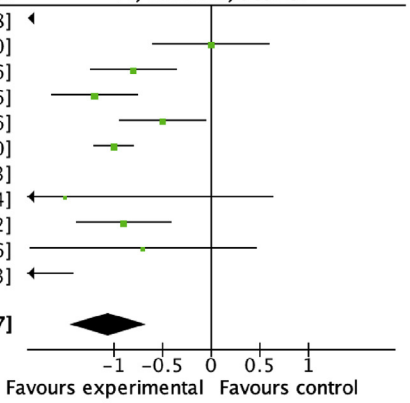
Heterogeneity: $Tau^2 = 0.19$; $Chi^2 = 28.83$, df = 6 ($P < 0.0001$); $I^2 = 79\%$
Test for overall effect: $Z = 4.68$ ($P < 0.00001$)



B

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Garcia 2013	1.6	2.1	10	6.3	2	12	3.8%	−4.70 [−6.42, −2.98]
Govil 2020	3.1	1	46	3.1	1.8	46	11.1%	0.00 [−0.60, 0.60]
Ibrahim 2018	3	0.6	20	3.8	0.8	20	12.6%	−0.80 [−1.24, −0.36]
Kim 2016	4.3	0.9	40	5.5	1.1	40	12.6%	−1.20 [−1.64, −0.76]
Maheshwari 2020	4.8	1.9	150	5.3	2	150	12.6%	−0.50 [−0.94, −0.06]
Murphy 2021	2	0.4	66	3	0.7	61	14.4%	−1.00 [−1.20, −0.80]
Nitta 2013	3.3	5.5	12	1.5	2.1	12	0.0%	1.80 [−1.53, 5.13]
Pacreau 2012	1.7	3	10	3.2	1.7	10	2.7%	−1.50 [−3.64, 0.64]
Raja 2019	4.5	1	47	5.4	1.4	50	12.2%	−0.90 [−1.38, −0.42]
Soffin 2020	2.3	2.4	24	3	1.6	23	6.4%	−0.70 [−1.86, 0.46]
Zhang 2021	2	0.4	31	4	1.6	32	11.4%	−2.00 [−2.57, −1.43]
Total (95% CI)			**444**			**444**	**100.0%**	**−1.06 [−1.45, −0.67]**

Heterogeneity: $Tau^2 = 0.26$; $Chi^2 = 47.22$, df = 9 ($P < 0.00001$); $I^2 = 81\%$
Test for overall effect: $Z = 5.34$ ($P < 0.00001$)



C

Study or Subgroup	Experimental Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Garcia 2013	1.6	2.1	10	6.3	2	12	0.0%	−4.70 [−6.42, −2.98]
Govil 2020	3.1	1	46	3.1	1.8	46	14.3%	0.00 [−0.60, 0.60]
Ibrahim 2018	3	0.6	20	3.8	0.8	20	17.0%	−0.80 [−1.24, −0.36]
Kim 2016	4.3	0.9	40	5.5	1.1	40	17.0%	−1.20 [−1.64, −0.76]
Maheshwari 2020	4.8	1.9	150	5.3	2	150	0.0%	−0.50 [−0.94, −0.06]
Murphy 2021	2	0.4	66	3	0.7	61	20.8%	−1.00 [−1.20, −0.80]
Nitta 2013	3.3	5.5	12	1.5	2.1	12	0.0%	1.80 [−1.53, 5.13]
Pacreau 2012	1.7	3	10	3.2	1.7	10	0.0%	−1.50 [−3.64, 0.64]
Raja 2019	4.5	1	47	5.4	1.4	50	16.3%	−0.90 [−1.38, −0.42]
Soffin 2020	2.3	2.4	24	3	1.6	23	0.0%	−0.70 [−1.86, 0.46]
Zhang 2021	2	0.4	31	4	1.6	32	14.7%	−2.00 [−2.57, −1.43]
Total (95% CI)			**250**			**249**	**100.0%**	**−0.99 [−1.37, −0.61]**

Heterogeneity: $Tau^2 = 0.17$; $Chi^2 = 24.35$, df = 5 ($P = 0.0002$); $I^2 = 79\%$
Test for overall effect: $Z = 5.12$ ($P < 0.00001$)

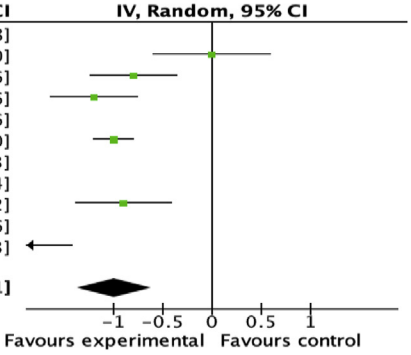


Figure 7. Forest plots demonstrating sub-group analysis.

significance of a decrease in pain scores of <10 on a scale of 0–100 mm.[41] A systematic review of minimum clinically important difference in acute pain identified a wide range of values from 8 to 40 mm (standardized to a 100-mm scale).[42] The investigators concluded that the minimum clinically important difference in the change in acute pain

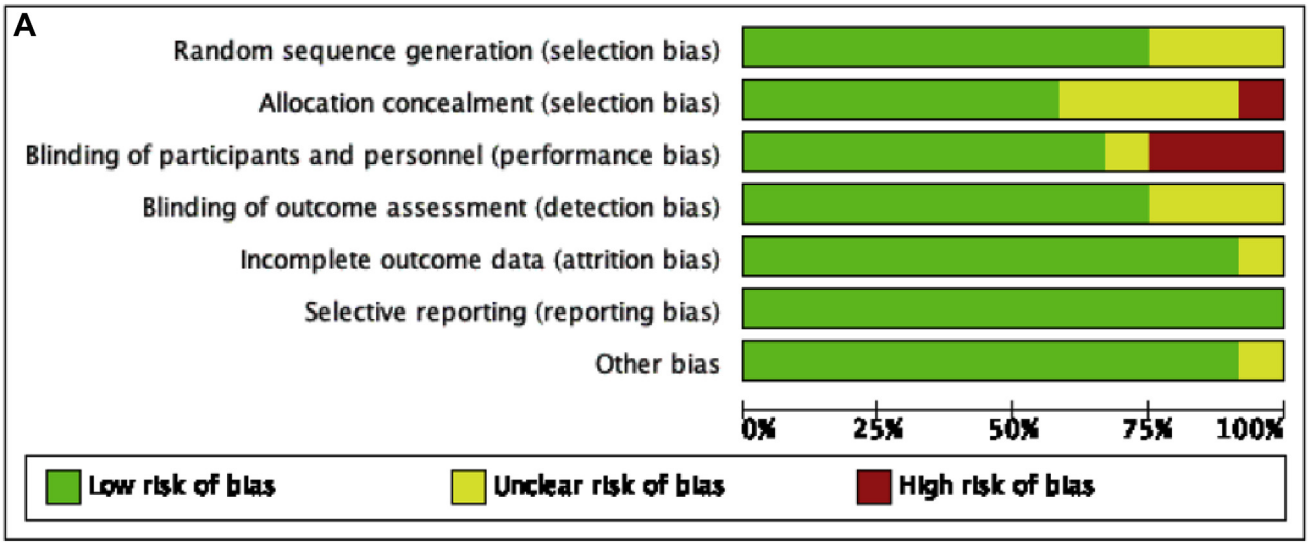


Figure 8. Risk of bias graph and summary in included studies.

(Continues)

depended on the baseline pain, definitions of improvement, and the study design. Other studies have identified a meaningful patient outcome measure of improvements in pain scores of 20%–45% as a minimum threshold.[43] Rather than considering a standalone numerical value, it might also be important to view the consistency of the analgesic parameter improvement, in conjunction with overall measures of the quality of care. We identified a smaller, but uniform, decrease in opioid requirements. This decrease in opioid requirements did not translate into a decrease in the side effect endpoints. We identified no differences between the intervention group and study group regarding the incidence of nausea and vomiting or respiratory events. Some of the studies had not reported on either of these outcomes.[32,31] This has limited the utility of our meta-analysis regarding the occurrence of adverse events. The theoretical advantages of multimodal analgesia include decreased side effects from opioid medication. We were unable to demonstrate this in our study. It is possible that an inadequate number of studies had included this outcome, and, as such, our meta-analysis was underpowered to demonstrate efficacy.

We identified considerable statistical heterogeneity across the primary and secondary outcomes (excluding the hospital length of stay, for which no statistical heterogeneity was identified). Multimodal analgesia relies conceptually on the synergism of various antinociceptive effects of administered medication. At present, although multimodal analgesia is thought to be the optimal approach, no rational strategy for choosing the drug combinations has been proposed.[44] It is not feasible to control for particular multimodal combinations in clinical practice. In addition, multimodal analgesia can be administered pre-, intra-, and/or postoperatively. We hypothesized that the individual agents used in various multimodal regimens would have some standalone activity. We, therefore, hypothesized that various pharmacological combinations would demonstrate efficacy. We used a quantitative model of maximal analgesia, instead of focusing on the specific qualitative interactions of medications. This qualitative variation introduced some clinical heterogeneity. We deliberately chose to include all and any oral and intravenous analgesics to conduct a real-world systematic review that would mirror active analgesic practice. When the studies at a high risk of bias were excluded, heterogeneity was found to be significantly less. We found moderate heterogeneity in the VAS scores at 24 hours with maintenance of the efficacy of multimodal analgesia. Therefore, heterogeneity in the present meta-analysis could have occurred because of underlying methodological issues in some of the included studies. This finding points to the methodological causes identified in the primary studies as a background factor in the statistical heterogeneity in the primary outcomes.

No meaningful statistical heterogeneity was calculated in the hospital length of stay outcome. The evidence for a substantial reduction in the hospital length of stay was high quality with low statistical heterogeneity. Our study was heterogeneous regarding the choice of multimodal analgesia. However, we found a consistent ability of any combination of the analgesia combinations used to decrease the hospital length of stay. The decreased length of stay is congruent with global improvement in the postoperative parameters with the use of multimodal analgesia. A longer than expected length of stay can be viewed as indicative of poor quality of care. Improvements in the length of stay have been considered to indicate the receipt of a

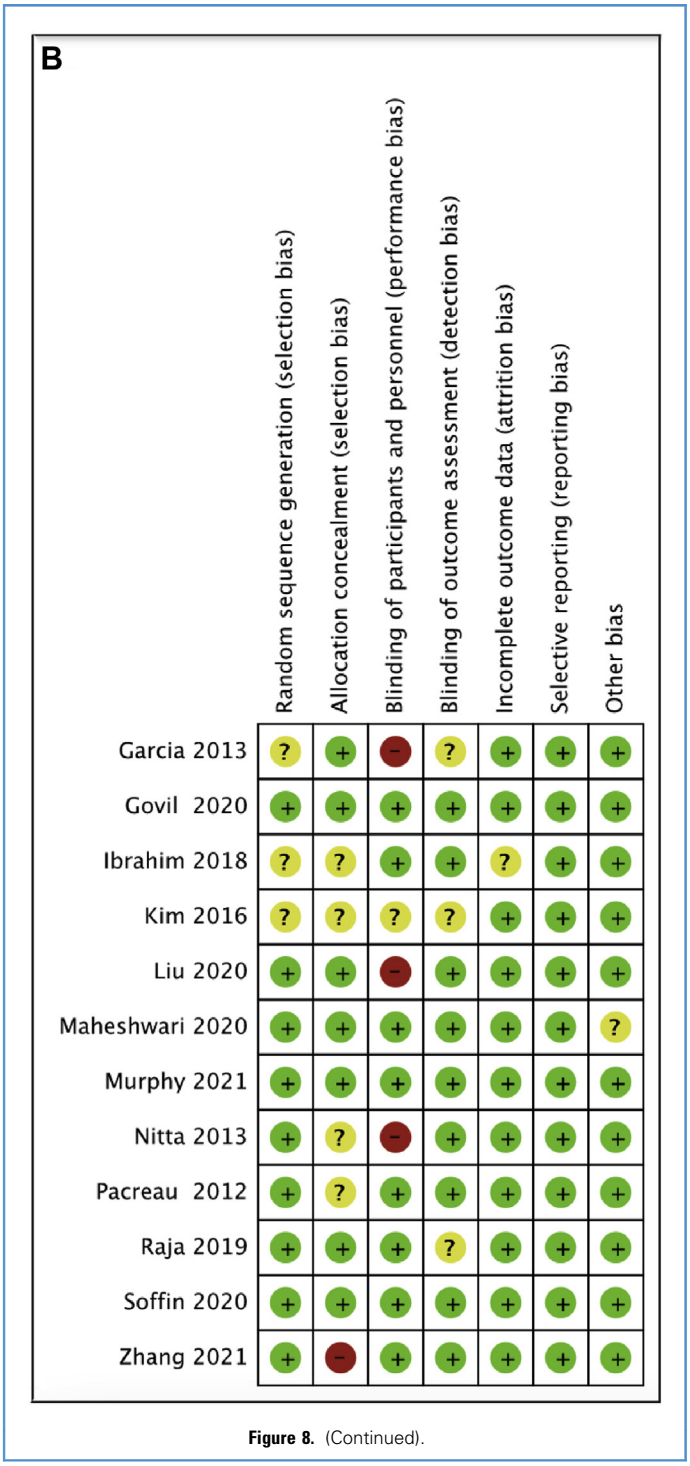


Figure 8. (Continued).

higher quality of care.[45] The length of stay has been seen by some proponents as an effective measure of the quality of care delivered.[46] Shorter admission periods have been associated with improved functional outcomes and lower mortality.[47] Decreasing the length of stay after spine surgery has been seen as an important step in decreasing the healthcare costs.[48]

We performed a single preplanned subgroup analysis of the patients who had undergone major surgery only. We identified no differences in the efficacy of multimodal analgesia when the patients who had undergone minor surgery were excluded. We were unable to compare the efficacy of multimodal analgesia between major and minor surgery owing to the paucity of data available for patients who had undergone minor surgery. To explore the causes of heterogeneity, we performed 2 further subgroup analyses: 1) a subgroup that excluded patients using α_2-blockers; and 2) a subgroup that excluded patients who had received ketamine. We postulated that intravenous ketamine might be more efficacious than the other components of multimodal analgesia. However, multimodal component therapy continued to be efficacious when the ketamine subgroup had been excluded, with ongoing statistical heterogeneity.

The purported advantages of multimodal analgesia include a decrease in the opioid side effect profile. Our study did not identify any differences in the outcome of nausea and vomiting and respiratory side effects in the group receiving multimodal analgesia. Our findings are in contrast to the postulations by several narrative reviews.[49] A comparable rate of analyzed adverse effects might have occurred because of optimal perioperative care and an inherently low risk of respiratory adverse events. A comparable rate of perioperative nausea and vomiting also could have occurred because this component could be affected by the use of volatile anesthesia or the side effects of multimodal analgesic therapy.

The limitations of our study findings relate to the limitations of the studies themselves. Some of the studies were small, which could have limited the generalizability of the treatment effects. In the present meta-analysis, we mitigated the risk of bias through the use of a second methodological quality assessment. Using the GRADE system, the evidence for the use of perioperative multimodal analgesia has been deemed as moderate to high quality across our primary and secondary outcomes. Maheshwari et al.[34] studied the effects of

multimodal analgesia on the postoperative quality of recovery. Lower doses of cumulative analgesic therapies were incorporated into the multimodal protocol. Furthermore, the statistical analysis and study plan were preset according to the quality of recovery outcomes. Therefore, our study might have been underpowered to report the true pain outcomes of multimodal analgesia. Soffin et al.[38] studied multimodal analgesia within enhanced recovery, which possibly resulted in a positive bias owing to the complex stepwise approach to analgesia. A number of our included studies had reported their secondary outcomes data as the median rather than as the mean. The data distribution had been presented as the interquartile range, which was transformed for our review.[19] This transformation introduced a risk of a statistical error.[50]

CONCLUSIONS

We have identified high-quality evidence for quantitative modeling of maximal multimodal analgesia to decrease the hospital length of stay for patients undergoing surgery of the spine. The treatment group had had consistently lower VAS scores by a clinically meaningful amount in the intermediate postoperative period after surgery of the spine. This finding was limited by high statistical heterogeneity for these outcomes; however, the heterogeneity appeared methodological in nature. Further high-quality studies using pain outcomes as the primary endpoints are needed to elucidate the most efficacious combination models of multimodal analgesia.

ACKNOWLEDGMENTS

Data will be available beginning 9 months and ending 36 months after study result publication. Data will be shared with investigators whose proposed use of the data has been approved by an independent review committee ("learned intermediary") identified for this purpose. Research proposals should be directed to analicina@hotmail.com. For access, data requestors will be required to sign a data access agreement.

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