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SYSTEMATIC REVIEW

Effects of Gabapentin on Postoperative Pain Management After Spinal Surgery: A Systematic Review and Meta-analysis

Muhammet Selman Söğüt[1], Merve Ümran Yılmaz[1], Mete Manici[1], Muhammet Ahmet Karakaya[2], Burcu Kılıçaslan Divanlıoğlu[3], Kamil Darçın[1]

[1]Department of Anesthesiology and Reanimation, Koç University Faculty of Medicine, İstanbul, Türkiye
[2]Department of Anesthesiology and Reanimation, Acıbadem University Faculty of Medicine, İstanbul, Türkiye
[3]Department of Anesthesiology and Reanimation, Ankara Bilkent City Hospital, Ankara, Türkiye

ABSTRACT

Effective postoperative pain management is pivotal for recovery, with an increasing focus on non-opioid analgesics. This study evaluates the efficacy of gabapentin in reducing postoperative opioid usage and pain after spinal surgeries in adults. We conducted a meta-analysis of prospective randomized placebo-controlled trials comparing preoperative gabapentin with placebo in adult spinal surgery patients. Primary outcomes included opioid consumption in the first 24 hours postoperatively, converted to oral morphine equivalents. Secondary outcomes assessed were Visual Analog Scale (VAS) pain scores and side effects within the same period. Thirteen of 674 studies met inclusion criteria, encompassing 843 participants. Gabapentin significantly decreased opioid consumption (mean difference [MD]: -39.91, 95% CI: -66.40 to -13.41; p=0.0069) and reduced VAS pain scores at various postoperative intervals, despite high heterogeneity (I^2=96.8%). Preoperative gabapentin reduces opioid consumption and early postoperative pain in spinal surgery patients. Further research is needed to ascertain the optimal dosing and potential impacts on postoperative complications.

Keywords: Gabapentin, meta-analysis, opioid, pain, postoperative complications, systematic review, visual analog scale

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INTRODUCTION

When the management of postoperative pain is inappropriate or unsuccessful, undesirable conditions such as myocardial ischemia, impaired pulmonary function, ileus, thromboembolism, delayed recovery time, prolonged opioid use, and impaired immune function may ensue.[1–4] Moreover, the presence and severity of acute pain during or after surgery can be a precursor to the development of chronic pain, which requires a more specific treatment approach.[5]

Despite the use of new medications and administration methods, studies have unfortunately demonstrated that postoperative pain remains inadequately managed.[6–8] After surgery, approximately 75% of patients experience acute pain, and their pain is of moderate to severe intensity in 80% of cases. Medical treatment is often initiated as a first-line management strategy. Opioid analgesics, the most effective option for medical treatment, remain the most commonly used drugs, despite their side effects, such as nausea, vomiting, itching, urinary retention, constipation, drowsiness, respiratory depression, hypotension, and bradycardia.[9–15]

For some surgeries, the side effects of opioids, such as nausea and vomiting, may not be tolerable. Therefore, in recent times, there has been increasing emphasis on the use of non-opioid analgesic drugs as components of multimodal

Address for Correspondence: Merve Ümran Yılmaz, Department of Anesthesiology and Reanimation, Koç University Faculty of Medicine, İstanbul, Türkiye
E-mail: merveumranyilmaz@gmail.com **ORCID ID:** 0009-0007-4754-8056

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analgesia protocols to relieve pain.[16–20] This approach has the potential to facilitate the early mobilization of surgical patients and contribute to their well-being.[21]

Gabapentin, a non-opioid, is an antiepileptic drug that has been shown to have analgesic efficacy in diabetic neuropathy, post-herpetic neuralgia, and neuropathic pain.[22,23] Although gabapentin itself is not an analgesic, it has attracted attention in recent years due to claims that it can enhance postoperative analgesia and reduce opioid requirements.[24] Gabapentin, which has antiallodynic and antihyperalgesic effects, reduces the hyperexcitability of dorsal horn neurons induced by surgical tissue injury.[25] However, the literature on gabapentin's effectiveness in postoperative pain control is controversial; while it has reported efficacy in spinal surgeries, it has been found to be ineffective after orthopedic and gynecological surgeries.[26,27]

In previous years, some meta-analyses have been conducted to evaluate the postoperative effects of gabapentin in spinal surgery.[28–31] According to these meta-analyses, gabapentin has been shown to reduce postoperative visual analog scale (VAS) scores and opioid consumption within 24 hours,[28,29] but some reports have highlighted the need for further studies to determine optimal dosing and dosing intervals.[30,31] Despite the large number of randomized controlled trials on gabapentin in recent years, there is no up-to-date meta-analysis. Due to the addition of randomized controlled trials to the literature and the previously mentioned conflicting results, a current need has arisen for a meta-analysis examining gabapentin's postoperative effects in spinal surgery. In this paper, we conducted a comprehensive meta-analysis and a systematic review examining the effects of gabapentin on postoperative pain after spinal surgery in adults in terms of opioid consumption, VAS scores, and postoperative complications in the first 24 hours.

MATERIALS and METHODS

A comprehensive meta-analysis was conducted adhering to the PRISMA guidelines to examine the effects of gabapentin on postoperative pain following spinal surgery in adults. A comprehensive search of PubMed, Scopus, CENTRAL, and MEDLINE databases was conducted at 06.02.2023 with the following keywords and logical operators:

1. TITLE-ABS-KEY ("gabapentin")
2. TITLE-ABS-KEY ("spinal surgery")
3. TITLE-ABS-KEY ("spinal stenosis")
4. TITLE-ABS-KEY ("pain")
5. 2 OR 3
6. 1 AND 4
7. Search: 5 AND 6

Prospective randomized placebo-controlled trials involving adult patients undergoing spinal surgery were included. The intervention of interest was the administration of gabapentin as a treatment for postoperative pain on the day of surgery, specifically before the procedure. Relevant outcomes for inclusion were opioid consumption, pain intensity as measured by the Visual Analog Scale (VAS) or a similar scale, and a range of postoperative complications such as nausea, vomiting, dizziness, sedation, pruritus, urinary retention, and headache within the first 24 hours post-surgery. There were no restrictions based on the language of publication or the publication year, and both published studies and conference abstracts were included.

Studies were excluded if they did not measure the outcomes of interest, or if they failed to report results for these outcomes and the authors did not provide the necessary information upon being contacted via e-mail.

For the synthesis of data, studies were categorized into groups based on whether patients received preemptive gabapentin for postoperative pain management (Intervention Group) or a placebo (Control Group).

Study Selection

The study selection process was performed using the Covidence platform, which facilitated screening and data extraction. The identification of included studies consisted of three steps:

1. Automatic duplicate removal: Covidence platform was used to automatically identify and remove duplicate records.
2. Title and abstract screening: Two independent reviewers (KD and MSS) screened the titles and abstracts of the identified records to assess their relevance to the review question. Any record considered potentially eligible by either reviewer was included for full-text review.
3. Full-text review: Two reviewers (KD and MSS) independently assessed the full text of each potentially eligible study for inclusion in the meta-analysis. Disagreements between the reviewers were resolved through discussion and, if necessary, by involving a third researcher (MAK) as an arbitrator.

Throughout the process, the two independent reviewers worked independently at each stage of screening. In cases where missing data were identified, the lead author of the respective study was contacted via email twice, with a 7-day interval between emails, to obtain or confirm relevant information.

If translation was required for abstracts or articles to determine their eligibility, professional translation services would have been used. However, no such translations were needed in this meta-analysis.

Data Extraction

KD and MSS independently extracted the data from each included study, ensuring accuracy and minimizing the risk of bias. In cases of disagreement between the reviewers, they first attempted to resolve the issue through discussion. If a consensus could not be reached, a third reviewer (MAK) acted as an arbitrator to resolve the disagreement.

No automation tools were used for data extraction, and all data were manually collected by the reviewers.

Outcome Measures

The primary outcome was opioid consumption within the first 24 hours following surgery, quantified by converting dosages to oral morphine equivalents. Secondary outcomes included the measurement of postoperative pain using the VAS or an equivalent scale across specific intervals: 0–6 hours, 6–12 hours, and 12–24 hours post-surgery. Additionally, an evaluation of postoperative side effects within the first 24 hours was conducted, covering nausea, vomiting, headache, dizziness, sedation, pruritus, and urinary retention.

All results compatible with each outcome domain in each study were sought. In cases where VAS scores were reported in time frames that differed from the predefined intervals, the highest VAS score that fell even partially within the predefined time frames was selected for inclusion in the meta-analysis.

No changes were made to the inclusion or definition of the outcome domains or to the processes used to select results within eligible domains. The primary outcome, opioid consumption within the first 24 hours post-surgery, was considered the most important outcome for interpreting the review's conclusions, as it reflects the analgesic efficacy of gabapentin in the context of postoperative pain management.

Assessment of Risk of Bias

To assess the risk of bias in the included studies, we utilized Cochrane's risk of bias tool, ROB2. Two independent reviewers (KD, MSS) assessed the risk of bias for each study. They worked independently to reduce the potential for bias in the assessment process. In cases of disagreement between the reviewers, they attempted to resolve the issue through discussion. If a consensus could not be reached, a third reviewer (MAK) acted as an arbitrator to resolve the disagreement.

Effect Measures and Data Synthesis

In the synthesis or presentation of results for each outcome, specific effect measures were utilized. Mean differences were applied to quantify variations in opioid consumption and Visual Analogue Scale (VAS) scores. For binary outcomes, such as the incidence of postoperative complications, risk ratios were employed to assess the relative occurrence of these events between the intervention and control groups.

No specific thresholds or ranges were used to interpret the size of the effect. Instead, the results were analyzed and interpreted based on the calculated effect measures and their clinical relevance.

In cases where a study included more than one intervention group with different doses or timings of gabapentin administration and only one placebo group, the intervention groups were pooled when calculating the overall effect of gabapentin to avoid unit-of-analysis errors (Formulas in Supplemental Digital Data – Section 1).

When a study reported opioid consumption in mg/kg or mcg/kg rather than milligrams or micrograms, and the mean and standard deviation (SD) of opioid consumption and weight of the patients in the group were provided, the data was converted to milligrams or micrograms (Formulas in Supplemental Digital Data – Section 2).

Following conversion factors were used to convert other opioids to oral morphine equivalents:

- IV Fentanyl (mcg): 0.3
- IV Hydromorphone (mg): 15
- IV Morphine (mg): 3
- IV Tramadol (mg): 0.2

Statistical Analysis

Statistical analysis was performed using R software v4.2.3 and meta, metafor, tidyverse and dmetar packages.

A random-effects model was employed to estimate the pooled effect sizes. Inverse variance method, the Hartung-Knapp adjustment, restricted maximum-likelihood estimator for τ^2 and the Q-Profile method for confidence intervals for τ^2 and τ were used.

The I2 statistic was calculated to determine the extent of variability among study results due to heterogeneity rather than chance. The H statistic was also computed to further assess the presence of heterogeneity. Prediction intervals (PI) were calculated based on the t-distribution to provide an interval within which the effect size of a future study is likely to fall.

Subgroup analyses were conducted to explore the potential sources of heterogeneity, as well as to compare the effect of different doses on the outcomes. A test for subgroup differences was conducted using the random-effects model to assess whether the pooled effects varied significantly among the subgroups.

For each outcome analyzed, forest plots were created to visualize the results. The results were reported with 95% confidence intervals (CIs) and p-values. A p-value of less than 0.05 was considered statistically significant.

The influence of individual studies on the overall effect estimate was evaluated by excluding each study one at a time and reanalyzing remaining studies. Influence diagnostics were used to evaluate the influence of each study on the overall effect by examining the studentized residuals, DFFITS value, Cook's distance, covariance ratio, Leave-one-out τ^2 and Cochran's Q values, hat value and study weight.

Influence diagnostics were carried out for each outcome measure to identify any influential or outlier studies. In cases where such studies were detected, a reanalysis was conducted, excluding those studies from the calculations. The results of both the primary analysis and the reanalysis were reported, offering a comprehensive understanding of the potential impact of influential or outlier studies on the overall findings.

Reporting Bias Assessment

Potential presence of publication bias was assessed through visual examination of funnel plots and the application of Egger's regression test.

The protocol for this study has been formally registered with PROSPERO. The assigned registration identification number for the study protocol is CRD42023423735.

RESULTS

674 studies were identified from the database searches. After removing 153 duplicates, 521 studies remained for screening. During the title and abstract screening stage, 471 studies were excluded, leaving 50 studies for full-text review. Following the full-text review, 37 studies were excluded based on the eligibility criteria. Ultimately, 13 studies.[32–44] were included in the systematic review and meta-analysis (Fig. 1, Table 1).

In the risk of bias assessment, the majority of the included studies demonstrated an overall low to moderate risk of bias. However, one study was identified as having a high risk of bias due to incomplete outcome data. Additionally, several studies raised some concerns regarding selective reporting, which could potentially impact the overall findings of the meta-analysis. Nevertheless, the general quality of the included studies was deemed acceptable for conducting the meta-analysis (Fig. 2).

Opioid Consumption in Postoperative First 24 Hours

A total of 12 studies were combined (k=12), with a total of 843 observations to analyze the effects of gabapentin on postoperative opioid consumption. The random-effects model demonstrated a significant reduction in opioid consumption in the gabapentin group compared to the placebo group, with a mean difference (MD) of -39.91 (95% CI: -66.40 to -13.41; t=-3.31; p=0.0069). The prediction interval for this analysis ranged from -129.27 to 49.46, indicating a substantial degree of uncertainty regarding the individual treatment effects in future studies (Fig. 3).

The heterogeneity analysis revealed a high level of inconsistency across the included studies. The τ^2 value was 1471.45 (95% CI: 679.92 to 5516.57), and the τ value was 38.36 (95% CI: 26.08 to 74.27). The I^2 statistic was 96.8% (95% CI: 95.6% to 97.6%), and the H value was 5.58 (95% CI: 4.77 to 6.52), further confirming the substantial heterogeneity among the analyzed studies.

The test of heterogeneity was highly significant with a Q value of 342.11, degrees of freedom (df) of 11, and a p-value of less than 0.0001.

Influence Analysis

The results of the leave-one-out analysis indicated that the pooled effect estimates remain significant and relatively consistent when each study is omitted in turn. The effect estimates ranged from -42.03 to -29.54, with the lower and upper limits of the 95% confidence intervals remaining negative (Table 2). The I^2 values continued to be high, ranging from 0.934 to 0.971, indicating that substantial heterogeneity among the included studies persists even after excluding individual studies.

Omitting the study conducted by Pandey et al.[36] led to a notable change in the pooled effect size, shifting it to -29.540.

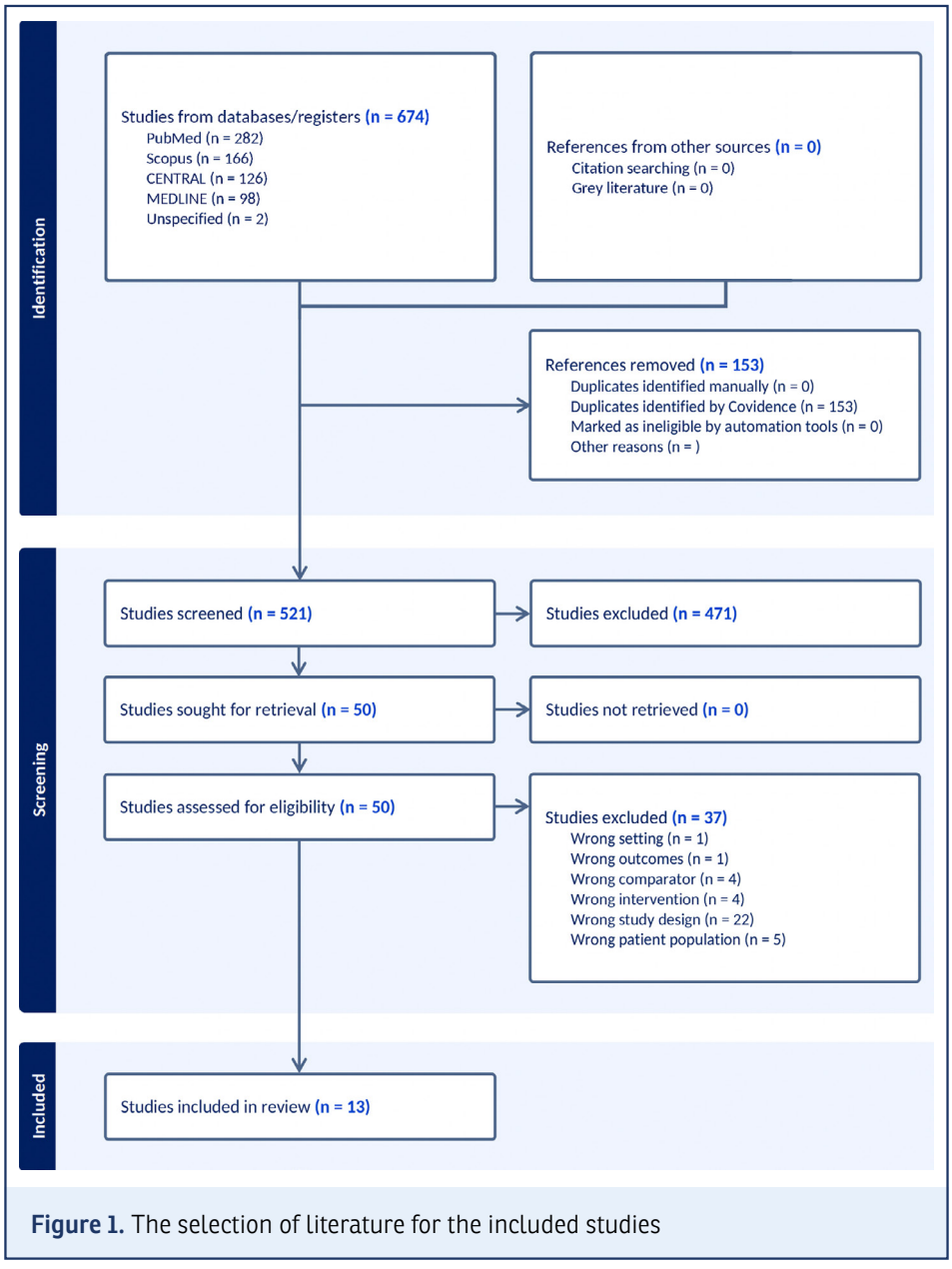

Figure 1. The selection of literature for the included studies

Influence diagnostics further highlighted the same study as a potential outlier or influential study, with the student value of -4.198, DFFITS value of -1.377, Cook's distance value of 0.783 (Fig. 4, Table 3).

Subgroup Analysis

Given that only a single study examined the effects of postoperative gabapentin administration, it was not feasible to perform a subgroup analysis based on the timing of gabapentin administration. Preoperative and postoperative gabapentin groups were pooled by dose for the dose-based subgroup analysis. For the primary analysis focusing on opioid consumption, all timings and doses were pooled.

A subgroup analysis of the studies was performed to explore the potential impact of different gabapentin doses on the opioid consumption (Fig. 5). Results are summarized in Table 4.

Subgroup analysis showed a trend suggesting that as the dose of gabapentin increases, there is a greater reduction in opioid doses used by patients. However, these observed reductions were not statistically significant in any of the subgroups, as indicated by the wide 95% confidence intervals that crossed zero. One potential explanation for the lack of statistical significance, despite the observed trend and the statistically significant result observed in the initial analysis without subgroups, could be the low number of studies included in each subgroup.

Table 1. Baseline characteristics of the included studies

Study	Gabapentin group (Dose - n)	Placebo group (n)
Erten et al.[32]	900 mg - 20	20
	1200 mg - 19	
Vahedi et al.[33]	300 mg - 36	40
Radhakrishnan et al.[34]	400 mg - 30	30
Leung et al.[35]	900 mg - 9	12
Pandey et al.[36]	300 mg – 20	20
	600 mg – 20	
	900 mg – 20	
	1200 mg - 20	
Khan et al.[37]	600 mg – 25	25
	900 mg – 25	
	1200 mg – 25	
Pandey et al.[38]	300 mg - 28	28
Ozgencil et al.[39]	600 mg - 30	30
Turan et al.[40]	1200 mg – 25	25
Vasigh et al.[41]	900 mg - 38	38
Routray et al.[42]	300 mg - 25	25
Khurana et al.[43]	300 mg - 30	30
Samarah et al.[44]	300 mg - 20	20

The test for subgroup differences under the random-effects model was significant (Q=12.65, df=4, p=0.0131), indicating that the effects vary significantly between these different dose subgroups.

Substantial heterogeneity was observed within each of the subgroups, evident through the high I2 statistics and substantial τ^2 values, indicating that a large proportion of the total variation in effect sizes is due to true differences between the studies, rather than random error.

VAS Scores between Postoperative 0–6 Hours

The random-effects model showed a significant reduction in VAS scores in the gabapentin group compared to the placebo group, with a mean difference of -1.40 (95% CI: -2.30 to -0.50; t=-3.51; p=0.0066). The prediction interval ranged from -4.26 to 1.46, indicating considerable uncertainty regarding the individual treatment effects in future studies (Supplemental Digital Data – Fig. 1). The heterogeneity analysis showed a high level of inconsistency across the included studies, with an I2 value of 90.8% (95% CI: 85.2% to 94.3%) and an H value of 3.30 (95% CI: 2.60 to 4.18). Influence analysis did not identify any influential or outlier studies.

VAS Scores between Postoperative 6–12 Hours

The random-effects model demonstrated a significant reduction in VAS scores in the gabapentin group, with an MD of -1.02 (95% CI: -1.63 to -0.41; t=-3.87; p=0.0047) (Supplemental Digital Data – Fig. 2). The prediction interval ranged from -2.80 to 0.75. Heterogeneity analysis revealed an I2 value of 84.2% (95% CI: 71.7% to 91.2%) and an H value of 2.52 (95% CI: 1.88; 3.37), indicating substantial heterogeneity among the included studies. Influence analysis did not identify any influential or outlier studies.

VAS between Postoperative 12–24 Hours

The random-effects model showed a significant reduction in VAS scores in the gabapentin group, with an MD of -0.85 (95% CI: -1.46 to -0.24; t=-3.30; p=0.0131) (Supplemental Digital Data – Fig. 3). The prediction interval ranged from -2.64 to 0.93. Heterogeneity analysis revealed an I2 value of 88.6% (95% CI: 79.8%; 93.5%) and an H value of 2.96 (95% CI: 2.22; 3.93), indicating considerable heterogeneity among the included studies.

Influence analysis identified Pandey et al.[36] as a potential outlier or influential study. Removing this study from the analysis resulted in the differences stated in Table 5.

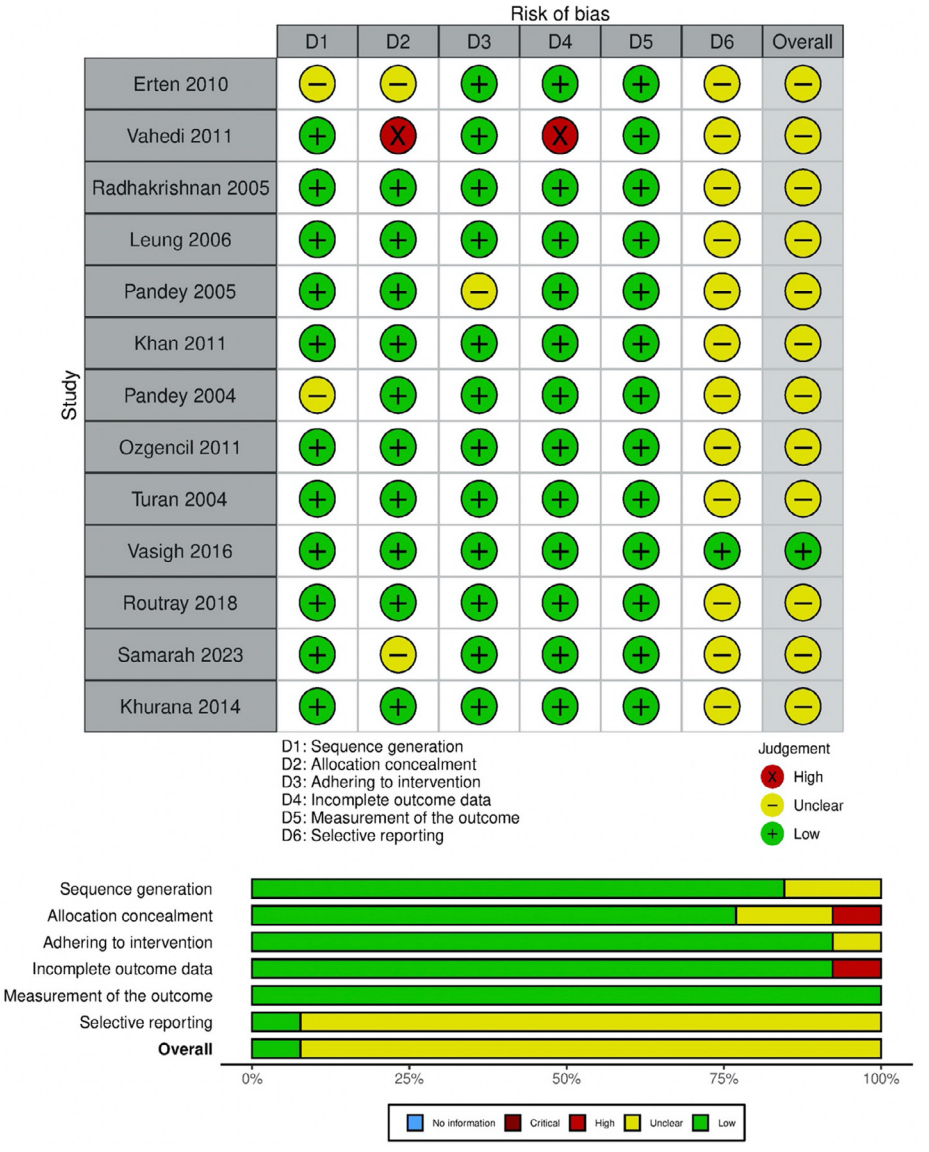

Figure 2. The summary of bias risk of studies

Complications

Nausea

The random-effects model showed a significant reduction in the risk of nausea with gabapentin, with an RR of 0.70 (95% CI: 0.51 to 0.97; t=-2.44; p=0.0348) (Supplemental Digital Data – Fig. 4). Heterogeneity was low with an I2 value of 0.0% (95% CI: 0.0% to 60.2%).

Influence analysis identified Vasigh et al.[41] and Samarah et al.[44] as potential outlier or influential studies. Upon excluding these studies from the analysis, the significant differences between groups were no longer observed (Table 6).

Vomiting

The random-effects model demonstrated a significant reduction in the risk of vomiting with gabapentin, with an RR of 0.54 (95% CI: 0.34 to 0.85; t=-3.14; p=0.0137) (Supplemental Digital Data – Fig. 5). Heterogeneity was low with an I2 value of 0.0% (95% CI: 0.0% to 64.8%). Influence analysis identified Vasigh et al.[41] as a potential outlier or influential study. Removing this study from the analysis resulted in the loss of significant differences between groups (Table 7).

Headache

No significant difference was found between gabapentin and placebo groups in terms of headache, with an RR of 1.19

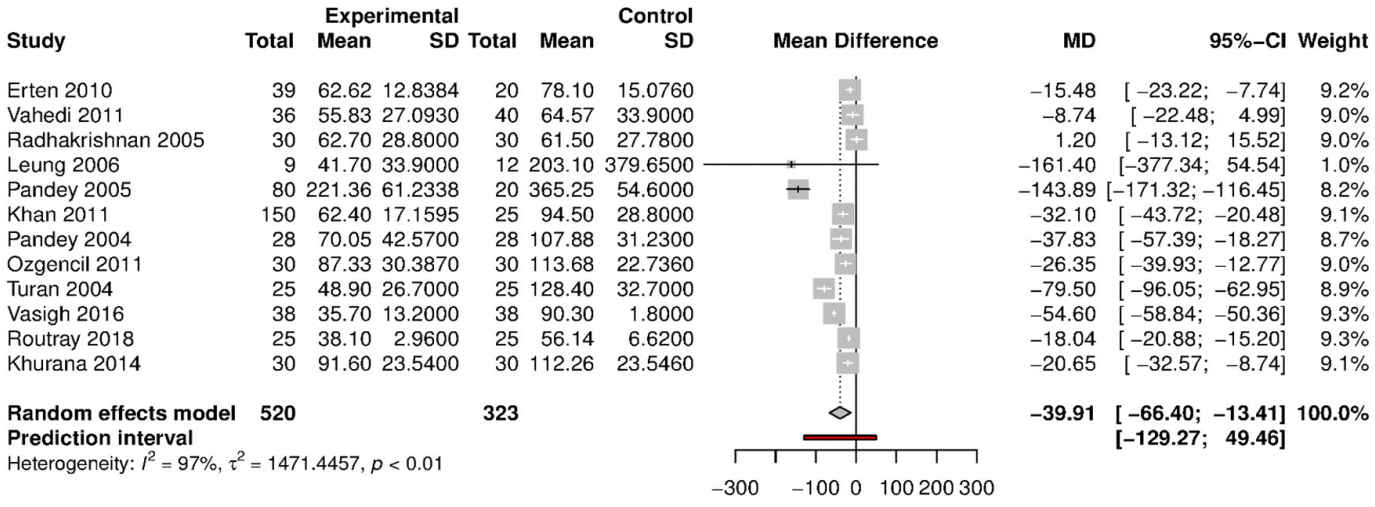

Figure 3. Forest plot for total opioid consumption in the postoperative first 24 hours

SD: Standard deviation; CI: Confidence interval

Table 2. Results of the leave-one-out analysis

	Effect	LLCI	ULCI	I²
Omitting Vasigh et al.[41]	-38.619	-68.129	-9.109	0.934
Omitting Routray et al.[42]	-42.331	-71.560	-13.102	0.956
Omitting Pandey et al.[36]	-29.540	-46.207	-12.873	0.963
Omitting Turan et al.[40]	-35.977	-63.942	-8.011	0.967
Omitting Radhakrishnan et al.[34]	-43.946	-71.827	-16.064	0.969
Omitting Erten et al.[32]	-42.550	-71.641	-13.458	0.970
Omitting Vahedi et al.[33]	-43.098	-71.769	-14.428	0.970
Omitting Leung et al.[35]	-38.666	-65.573	-11.758	0.971
Omitting Khan et al.[37]	-40.938	-70.591	-11.285	0.971
Omitting Pandey et al.[38]	-40.353	-70.004	-10.702	0.971
Omitting Ozgencil et al.[39]	-41.482	-70.994	-11.971	0.971
Omitting Khurana et al.[43]	-42.033	-71.355	-12.711	0.971

LLCI: lower limit confidence interval; ULCI: upper limit confidence interval.

(95% CI: 0.02 to 62.37; t=0.19; p=0.8661) (Supplemental Digital Data – Fig. 6). Heterogeneity was moderate with an I2 value of 47.4% (95% CI: 0.0% to 84.6%). Influence analysis did not identify any influential or outlier studies.

Dizziness

The random-effects model demonstrated a significant increase in the risk of dizziness with gabapentin, with an RR of 1.38 (95% CI: 1.00 to 1.91; t=2.45; p=0.0498). (Supplemental Digital Data – Fig. 7) Heterogeneity was low with an I2 value of 0.0% (95% CI: 0.0% to 70.8%). The prediction interval ranged from 0.78 to 1.91, indicating a considerable degree of uncertainty regarding the individual treatment effects in future studies. Influence analysis did not identify any influential or outlier studies.

Sedation

The random-effects model showed a significantly higher risk of sedation with gabapentin, with an RR of 2.58 (95% CI: 1.41 to 4.74; t=3.61; p=0.0069). Heterogeneity was low with an I2 value of 0.0% (95% CI: 0.0% to 64.8%) (Supplemental Digital Data – Fig. 8).

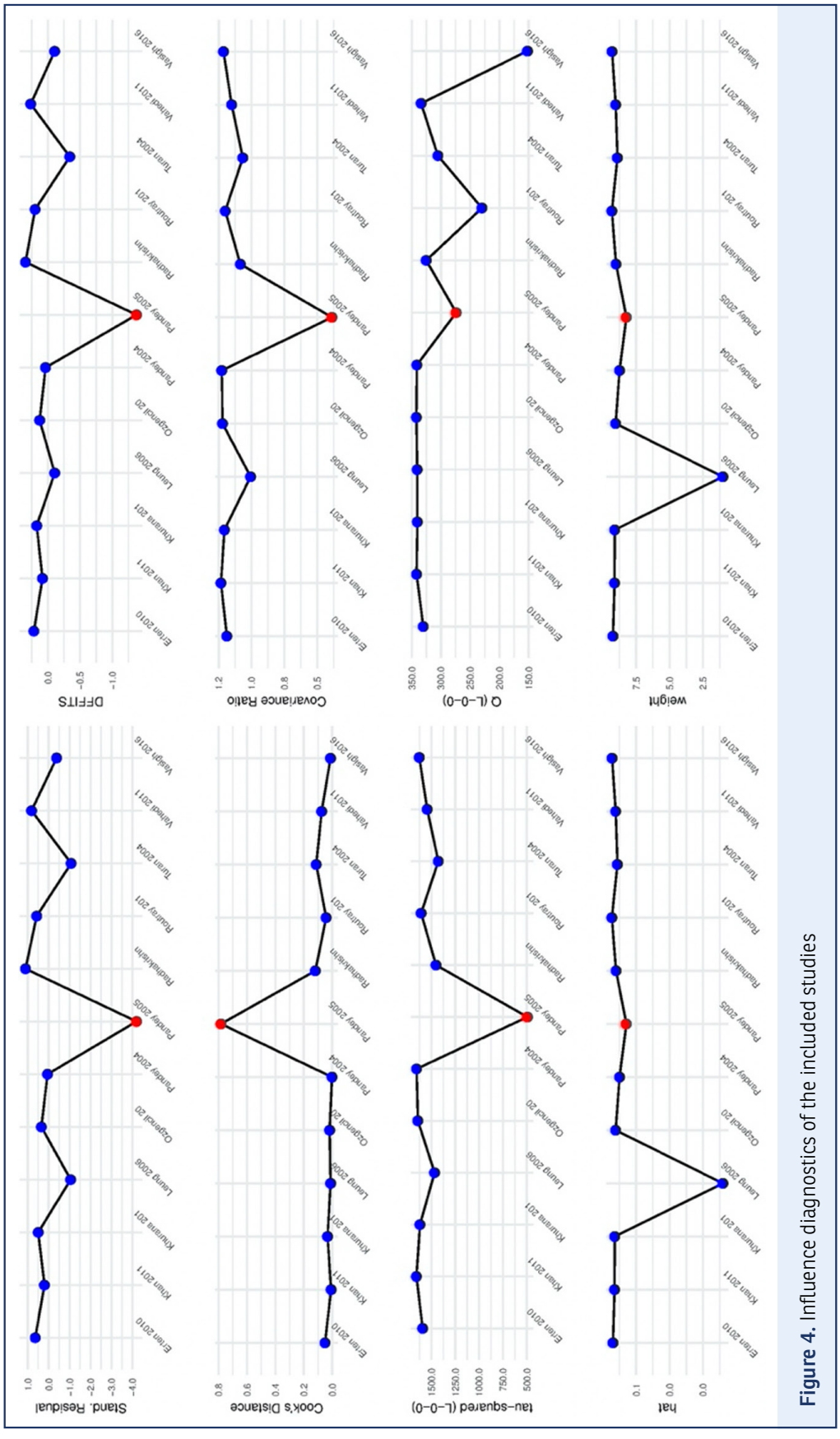

Figure 4. Influence diagnostics of the included studies

Table 3. The pooled effect sizes

	MD	95% CI	p	%95 PI	I^2	95% CI
Main analysis	-39.90	-66.40; -13.41	0.0069	-129.27; 49.46	97%	95.6; 97.7
Pandey et al.[36] removed	-29.54	-46.21;-12.87	0.0027	-82.39;b23.32	96%	94.9; 97.4

MD: Mean difference; CI: confidence interval; PI: prediction interval

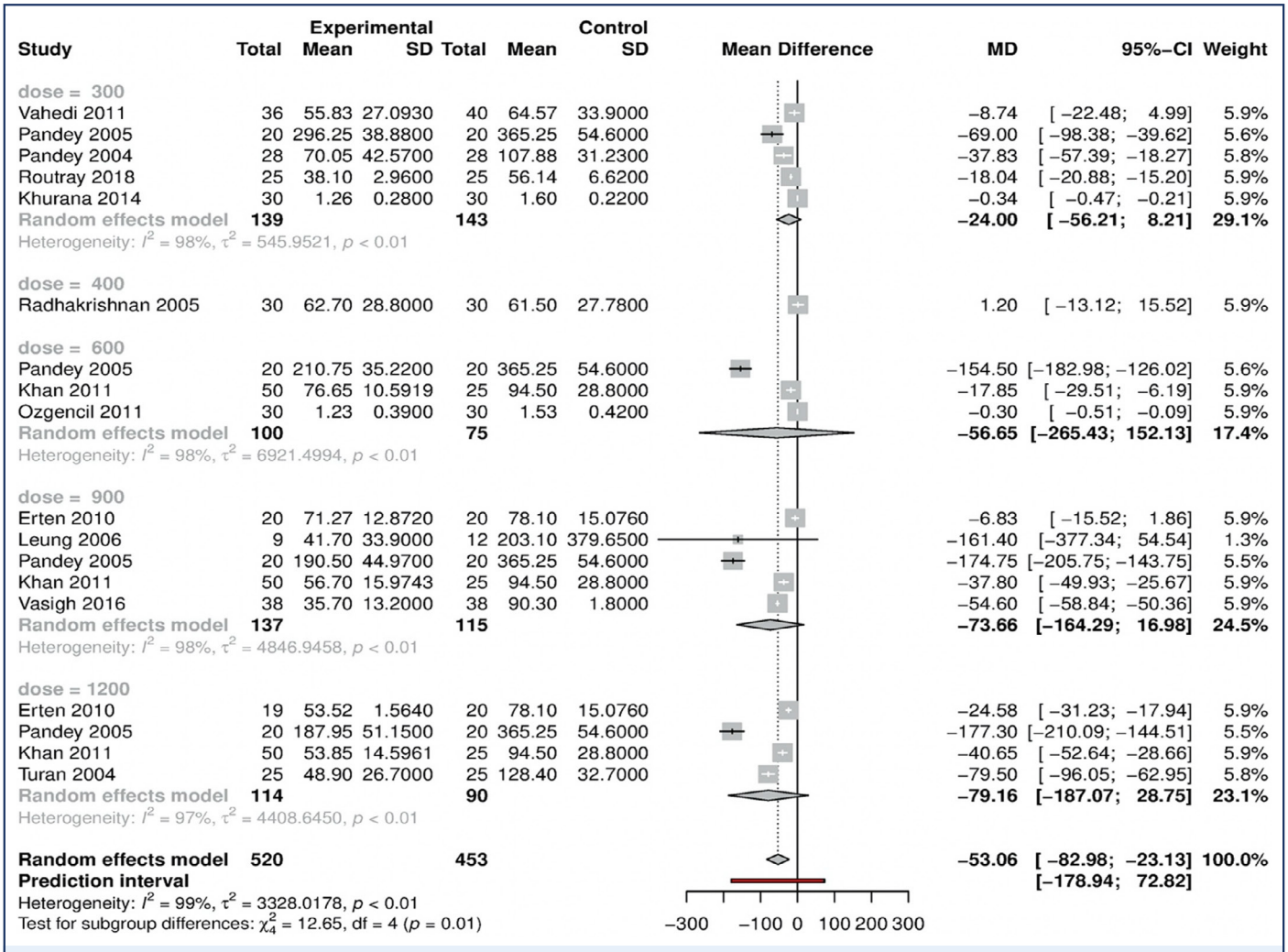

Figure 5. Subgroup analysis by dose (mg) for opioid consumption in the postoperative first 24 hours

SD: Standard deviation; CI: Confidence interval

Influence analysis identified Vasigh et al.[41] and Ozgencil et al.[39] as potential outlier or influential studies. Removing these studies from the analysis resulted in the differences stated in Table 8.

Pruritus

The random-effects model demonstrated a significant reduction in the risk of pruritus with gabapentin, with an RR of 0.38 (95% CI: 0.29 to 0.51; t=-10.97; p=0.0016). Heterogeneity was low with an I2 value of 0.0% (95% CI: 0.0% to 84.7%) (Supplemental Digital Data – Fig. 9). Influence analysis did not identify any influential or outlier studies.

Urinary retention

No significant difference was found between gabapentin and placebo groups in terms of urinary retention, with an

Table 4. Potential impact of different gabapentin doses

Dose	k	MD	95% CI	tau²	tau	Q	I²
300 mg	5	-24.00	-56.21; 8.21	546.0	23.37	185.12	98%
400 mg	1	1.20	-13.12; 15.52				
600 mg	3	-56.65	-265.43; 152.13	6921.5	83.20	121.33	98%
900 mg	5	-73.66	-164.29; 16.975	4846.9	69.62	162.95	98%
1200 mg	4	-79.16	-187.07; 28.75	4408.6	66.40	109.34	97%

MD: Mean difference; CI: confidence interval

Table 5. Mean difference change of VAS after removing outliers

	MD	95% CI	p	%95 PI	I²	95% CI
Main analysis	-0.85	-1.46; -0.24	0.0131	-2.64; 0.93	89%	79.8; 93.5
Pandey et al.[36] removed	-0.59	-0.85; -0.34	0.0013	-1.00; -0.19	38.2%	0; 74

MD: Mean difference; CI: Confidence interval; PI: Prediction interval

Table 6. Relative risk change of nausea after removing outliers

	RR	95% CI	p	%95 PI	I²	95% CI
Main analysis	0.70	0.51; 0.97	0.0348	0.50; 0.99	0%	0; 60
Influentials removed*	0.95	0.78; 1.16	0.61	0.60; 1.52	0%	0; 65

*: Vasigh et al.[41] and Samarah et al.[44]. RR: Relative risk; CI: Confidence interval; PI: Prediction interval

Table 7. Relative risk change of vomiting after removing outliers

	RR	95% CI	p	%95 PI	I²	95% CI
Main analysis	0.54	0.34; 0.85	0.0137	0.30; 0.98	0%	0;65
Influentials removed*	0.67	0.45; 1.00	0.0513	0.33; 1.35	0%	0; 68

*: Vasigh et al.[41] 2016. RR: Relative risk; CI: Confidence interval; PI: Prediction interval

Table 8. Relative risk change of sedation after removing outliers

	RR	95% CI	p	%95 PI	I²	95% CI
Main analysis	2.58	1.41; 4.74	0.0069	1.23; 5.42	0%	0; 65
Influentials removed*	2.38	1.17; 4.84	0.0248	0.69; 8.15	0%	0; 71

*: Vasigh et al.[41] and Ozgencil et al.[39] RR: Relative risk; CI: Confidence interval; PI: prediction interval

Table 9. Relative risk change of urinary retention after removing outliers

	RR	95% CI	p	%95 PI	I2	95% CI
Main analysis	0.61	0.20; 1.87	0.2559	0.07; 5.68	25%	0; 71
Influentials removed*	0.45	0.12; 1.64	0.1170	0.005; 43.4	0%	0; 90

*: Radhakrishnan et al.[34] RR: Relative risk; CI: Confidence interval; PI: Prediction interval

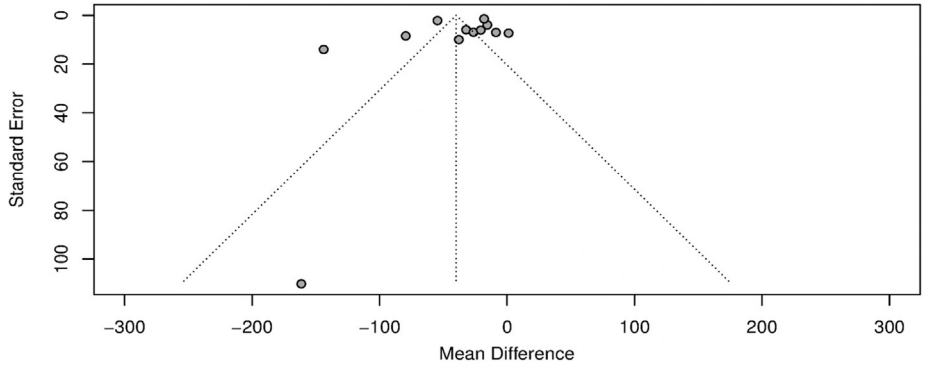

Figure 6. Funnel plot of included studies

RR of 0.61 (95% CI: 0.20 to 1.87; t=-1.40; p=0.2559). Heterogeneity was low with an I2 value of 25.2% (95% CI: 0.0% to 71.2%) (Supplemental Digital Data – Fig. 10).

Influence analysis identified Radhakrishnan et al.[34] as a potential outlier or influential study. Removing this study from the analysis resulted in the differences stated in Table 9.

Publication Bias

In order to assess publication bias in the meta-analysis, a linear regression test of funnel plot asymmetry was conducted (Fig. 6).

Egger's regression test results showed no significant evidence of publication bias (t=-0.75, df=10, p=0.4678). The sample estimates for the bias and intercept were -1.86 (se. bias=2.46) and -7.84 (se.intercept=3.01), respectively. The analysis used multiplicative residual heterogeneity variance (tau2=32.36), with the predictor being the standard error and the weight being the inverse variance.

DISCUSSION

In this systematic review and meta-analysis, the results of 13 prospective randomized studies have been compiled. It was found that, compared to placebo, perioperative administration of gabapentin reduces morphine consumption and Visual Analog Scale (VAS) scores in the first 24 hours postoperatively. Observations indicated that gabapentin increases the level of sedation and dizziness among postoperative complications, while decreasing itching. No significant differences were found in terms of nausea, vomiting, headache or urinary retention.

Gabapentin, an antiepileptic drug, is a 3-alkylated analog of gamma-aminobutyric acid (GABA) and modulates calcium ion channel subunits.[45] Gabapentin binds postsynaptically to the alpha-2-delta subunit of voltage-gated calcium channels in dorsal horn neurons, reducing calcium influx. This leads to a decreased release of excitatory neurotransmitters such as glutamate, substance P, and noradrenaline from nerve endings, providing anti-hyperalgesia.[46–49]

Opioids mimic the effects of endogenous opioid peptides, closing calcium channels and opening calcium-dependent inwardly rectifying potassium channels. This results in hyperpolarization and a decrease in neuronal excitability. They also reduce intracellular cAMP, which modulates the release of nociceptive neurotransmitters like substance P.[50] The co-administration of gabapentin and opioid significantly inhibits neuronal responses.[51]

This meta-analysis, encompassing 12 studies with a total of 843 observations, revealed a significant reduction in opioid consumption in the gabapentin group compared to the placebo group, with a mean difference of -39.91mg oral morphine equivalent. Notably, in the analysis, it was found that the 24-hour opioid consumption in the Pandey et al.[38] study appears higher than in other studies.[22–23]

This might be due to the study using a patient-controlled analgesia (PCA) demand dose, which could be considered high at 1 mcg/kg. When this study was excluded and the analysis was redone, there was still a decrease of 29.9 mg in oral morphine equivalent in the first 24 hours post-surgery.

In the subgroup analysis by dose, even though opioid use appeared to decrease with every dose, no statistically significant results were found. This could be attributed to the limited number of studies. Similar to the reduction in opioid requirement, we found a statistically significant reduction in VAS scores in the 0–6, 6–12, and 12–24-hour intervals.

Another objective of our study was to assess postoperative complications. The co-administration of gabapentin and opioids increased sedation and dizziness levels while reducing itching. There was no significant difference in terms of nausea, vomiting, headache or urinary retention.

Moreover, it has been suggested that gabapentin might prevent vomiting by reducing tachykinin neurotransmitter activity, unlike opioids.[22] However, there are conflicting reports in literature regarding these effects.[52] Although the analysis that included all studies indicated that gabapentin reduced nausea, after reviewing studies with outlier values and reanalyzing, high rates of nausea were observed in the placebo groups of the Vasigh et al.[41] and Samarah et al.[44] studies. After excluding these two studies from the analysis, it was concluded that gabapentin didn't influence nausea. Similarly, while a decrease in vomiting was observed when all studies were considered, no significant difference was found once the Vasigh et al.[41] study was excluded. In the Vasigh et al.[41] study, it is noteworthy that the frequency of vomiting in the placebo group was found to be higher compared to the placebo groups of all the other studies (34.5% compared to 16.2%).

Our analysis showed a reduced opioid use; however, it was intriguing that nausea and vomiting remained unchanged with the co-administration of gabapentin and opioids. Hence, there is a clear need for larger, prospective randomized studies with broader patient populations, where the side effect profile can be quantitatively assessed and compared.

Limitations

This meta-analysis exhibits substantial heterogeneity among the included studies, as indicated by high I^2 statistics, affecting the validity of pooled results. Although most studies had low to moderate bias risk, one had a high risk due to incomplete outcome data, and several showed concerns about selective reporting. The small number of studies in the overall meta-analysis and various subgroups limits statistical power. The studies used diverse gabapentin doses, contributing to the observed heterogeneity, and subgroup analysis to address this was inconclusive, possibly due to limited study numbers in each subgroup. The influence analysis revealed that the results are sensitive to specific studies, such as Pandey et al.,[36] being included or excluded, implying potential bias in the overall findings. Wide prediction intervals in the primary analysis signify significant uncertainty in future effect size estimates.

Gabapentin, when administered preoperatively, is associated with a significant reduction in postoperative opioid consumption and pain intensity in patients undergoing spinal surgery. The optimal dose of gabapentin and its effect on postoperative complications require further investigation due to the non-significant trends observed in the subgroups and potential reporting biases in the included studies.

Disclosures

Supplemental Digital Data: https://jag.journalagent.com/cm/abs_files/CM-57441/CM-57441_(2)_CM-57441_Supplemental_Digital_Data.pdf

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REFERENCES

1. Meara JG, Leather AJ, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet 2015;386:569–624. [CrossRef]
2. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res 2017;10:2287–98. [CrossRef]
3. Cohen SP, Christo PJ, Moroz L. Pain management in trauma patients. Am J Phys Med Rehabil 2004;83:142–61. [CrossRef]
4. Carr DB, Goudas LC. Acute pain. Lancet 1999;353:2051–8. [CrossRef]
5. Macrae WA. Chronic post-surgical pain: 10 years on. Br J Anaesth 2008;101:77–86. [CrossRef]
6. Apfelbaum JL, Chen C, Mehta S, Gan TJ. Postoperative pain experience: results from a national survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003;97:534–40. [CrossRef]
7. Warfield CA, Kahn CH. Acute pain management: programs in U.S. hospitals and experiences and attitudes among U.S. adults. Anesthesiology 1995;83:1090–4. [CrossRef]
8. Block BM, Liu SS, Rowlingson AJ, Cowan AR, Cowan JA Jr, Wu CL. Efficacy of postoperative epidural analgesia: a meta-analysis. JAMA 2003;290:2455–63. [CrossRef]
9. Wheeler M, Oderda GM, Ashburn MA, Lipman AG. Adverse events associated with postoperative opioid analgesia: a systemic review. J Pain 2002;3:159–80. [CrossRef]
10. Oderda GM, Evans RS, Lloyd J, Lipman A, Chen C, Ashburn M, et al. Cost of opioid-related adverse drug events in surgical patients. J Pain Symptom Manage 2003;25:276–83. [CrossRef]
11. Austrup ML, Korean G. Analgesic agents for the postoperative period. Opioids. Surg Clin North Am 1999;79:253–73. [CrossRef]
12. Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritus, and urinary retention. Evidence from published data. Br J Anaesth 2005;95:584–91. [CrossRef]

13. Pavlin DJ, Chen C, Penaloza DA, Polissar NL, Buckley FP. Pain as a factor complicating recovery and discharge after ambulatory surgery. Anesth Analg 2002;95:627–34. [CrossRef]
14. Sun XL, Zhao ZH, Ma JX, Li FB, Li YJ, Meng XM, et al. Continuous local infiltration analgesia for pain control after total knee arthroplasty: a meta-analysis of randomized controlled trials. Medicine (Baltimore) 2015;94:e2005. [CrossRef]
15. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Opioid complications and side effects. Pain Physician 2008;11:105–20. [CrossRef]
16. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology 2000;93:1123–33. [CrossRef]
17. Clarke H, Poon M, Weinrib A, Katznelson R, Wentlandt K, Katz J. Preventive analgesia and novel strategies for the prevention of chronic post-surgical pain. Drugs 2015;75:339–51. [CrossRef]
18. Lirk P, Rathmell JP. Opioid-free anaesthesia: con: it is too early to adopt opioid-free anaesthesia today. Eur J Anaesthesiol 2019;36:250–4. [CrossRef]
19. Harkouk H, Fletcher D, Beloeil H. Opioid free anaesthesia: myth or reality? Anaesth Crit Care Pain Med 2019;38:111–2. [CrossRef]
20. Pitchon DN, Dayan AC, Schwenk ES, Baratta JL, Viscusi ER. Updates on multimodal analgesia for orthopedic surgery. Anesthesiol Clin 2018;36:361–73. [CrossRef]
21. Kehlet H, Dahl JB. Anaesthesia, surgery, and challenges in post operative recovery. Lancet 2003;362:1921–8. [CrossRef]
22. Pandey CK, Priye S, Ambesh SP, Singh S, Singh U, Singh PK. Prophylactic gabapentin for prevention of postopretive nausea and vomiting in patients undergoing laparoscopic cholesystectomy. A randomized double blind, placebo controlled study. J Postgrad Med 2006;52:97–100.
23. Serpell MG. Gabapentin in neuropathic pain syndromes: a randomised, doubleblind, placebo-controlled trial. Pain 2002;99:557–66. [CrossRef]
24. Dahl JB, Mathiesen O, Moiniche S. 'Protective premedication': an option with gabapentin and related drugs? A review of gabapentin and pregabalin in in the treatment of post-operative pain. Acta Anaesthesiol Scand 2004;48:1130–6. [CrossRef]
25. Tiippana E, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anaesth Analg 2007;104:1545–56. [CrossRef]
26. Kang J, Zhao Z, Lv J, Sun L, Lu B, Dong B, et al. The efficacy of perioperative gabapentin for the treatment of postoperative pain following total knee and hip arthroplasty: a meta-analysis. J Orthop Surg Res 2020;15:332. [CrossRef]
27. Gray BA, Hagey JM, Crabtree D, Wynn C, Weber JM, Pieper CF, et al. Gabapentin for perioperative pain management for uterine aspiration: a randomized controlled trial. Obstet Gynecol 2019;134:611–9. [CrossRef]
28. Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine 2013;38:1947–52. [CrossRef]
29. Han C, Kuang MJ, Ma JX, Ma XL. The efficacy of preoperative gabapentin in spinal surgery: a meta-analysis of randomized controlled trials. Pain Physician 2017;20:649–61. [CrossRef]
30. Liu B, Liu R, Wang L. A meta-analysis of the preoperative use of gabapentinoids for the treatment of acute postoperative pain following spinal surgery. Medicine 2017;96:e8031. [CrossRef]
31. Peng C, Li C, Qu J, Wu D. Gabapentin can decrease acute pain and morphine consumption in spinal surgery patients: a meta-analysis of randomized controlled trials. Medicine 2017;96:e6463. [CrossRef]
32. Erten E, Bilgin F, Çekmen N, Özhan MÖ, Orhan ME, Kurt E. The analgesic effect of different doses of preemptive gabapentin preoperatively on patients undergoing elective laminectomy during postoperative period. Anestezi Derg [Article in Turkish] 2010;18:99–105.
33. Vahedi P, Shimia M, Aghamohammadi D, Mohajernezhadfard Z, Shoeibi A, Lotfinia I, et al. Does preemptive gabapentin reduce morphine consumption and remaining leg pain after lumbar discectomy? Neurosurg Q 2011;21:114–20. [CrossRef]
34. Radhakrishnan M, Bithal PK, Chaturvedi A. Effect of preemptive gabapentin on postoperative pain relief and morphine consumption following lumbar laminectomy and discectomy: a randomized, double-blinded, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:125–8. [CrossRef]
35. Leung JM, Sands LP, Rico M, Petersen KL, Rowbotham MC, Dahl JB, et al. Pilot clinical trial of gabapentin to decrease postoperative delirium in older patients. Neurology 2006;67:1251–3. [CrossRef]
36. Pandey CK, Navkar DV, Giri PJ, Raza M, Behari S, Singh RB, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blind, placebo-controlled study. J Neurosurg Anesthesiol 2005;17:65–8. [CrossRef]
37. Khan ZH, Rahimi M, Makarem J, Khan RH. Optimal dose of pre-incision/post-incision gabapentin for pain relief following lumbar laminectomy: a randomized study. Acta Anaesthesiol Scand 2011;55:306–12. [CrossRef]
38. Pandey CK, Sahay S, Gupta D, Ambesh SP, Singh RB, Raza M, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Can J Anaesth 2004;51:986–9. [CrossRef]
39. Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y. Perioperative administration of gabapentin 1,200 mg day-1 and pregabalin 300 mg day-1 for pain following lumbar laminectomy and discectomy: a randomised, double-blinded, placebo-controlled study. Singapore Med J 2011;52:883–9.
40. Turan A, Karamanlioğlu B, Memiş D, Hamamcioglu MK, Tükenmez B, Pamukçu Z, et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004;100:935–8. [CrossRef]
41. Vasigh A, Jaafarpour M, Khajavikhan J, Khani A. The effect of gabapentin plus celecoxib on pain and associated complications after laminectomy. J Clin Diagn Res 2016;10:4–8. [CrossRef]
42. Routray SS, Pani N, Mishra D, Nayak S. Comparison of pregabalin with gabapentin as preemptive analgesic in lumbar spine surgery. J Anaesthesiol Clin Pharmacol 2018;34:232–6. [CrossRef]
43. Khurana G, Jindal P, Sharma JP, Bansal KK. Postoperative pain and long-term functional outcome after administration of gabapentin and pregabalin in patients undergoing spinal surgery. Spine 2014;39:e363–8. [CrossRef]
44. Samarah BM, Shehada FA, Qaddumi J, Almasry NA, Alkhawaldeh A, AL-Bashtawy M, et al. A comparison of the preemptive effects of oral pregabalin and gabapentin on acute postoperative sedation and complications in patients undergoing lumbar spine surgery. J Perioper Pract 2023;33:358–64. [CrossRef]
45. Nicholson B. Gabapentin use in neuropathic pain syndromes. Acta Neurol Scand 2000;101:359–71. [CrossRef]
46. Qin N, Yagel S, Momplaisir ML, Codd EE, D'Andrea MR. Molecular cloning and characterization of the human voltage-gated calcium channel alpha(2)delta-4 subunit. Mol Pharmacol 2002;62:485–96. [CrossRef]
47. Maneuf YP, Gonzalez MI, Sutton KS, Chung FZ, Pinnock RD, Lee K. Cellular and molecular action of the putative GABA-mimetic, gabapentin. Cell Mol Life Sci 2003;60:742–50. [CrossRef]

48. Taylor CP, Gee NS, Su TZ, Kocsis JD, Welty DF, Brown JP, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. Epilepsy Res 1998;29:233–49. [CrossRef]

49. Gee NS, Brown JP, Dissanayake VU, Offord J, Thurlow R, Woodruff GN. The novel anticonvulsant drug, gabapentin (neurontin), binds to the a2d subunits of calcium channel. J Biol Chem 1996;271:5768–76. [CrossRef]

50. Bovill JG. Mechanisms of actions of opioids and non-steroidal anti-inflammatory drugs. Eur J Anaesthesiol Suppl 1997;15:9–15. [CrossRef]

51. Matthews EA, Dickenson AH. A combination of gabapentin and morphine mediates enhanced inhibitory effects on dorsal horn neuronal responses in a rat model of neuropathy. Anesthesiology 2002;96:633–40. [CrossRef]

52. Guttuso T Jr. Gabapentin's anti-nausea and anti-emetic effects: a review. Exp Brain Res 2014;232:2535–9. [CrossRef]