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

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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 (I²=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

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
analgesia protocols to relieve pain.[18–20] 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 following 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.

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 $\tau^2$ and the Q-Profile method for confidence intervals for $\tau^2$ and $\tau$ 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, DF-FITS value, Cook’s distance, covariance ratio, Leave-one-out τ² 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 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 τ² value was 1471.45 (95% CI: 679.92 to 5516.57), and the t value was 38.36 (95% CI: 26.08 to 74.27). The I² 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 I² 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. led to a notable change in the pooled effect size, shifting it to -29.540.
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.

**Figure 1.** The selection of literature for the included studies
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 τ² 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 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=0.0031) (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.
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 I^2 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 I^2 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
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(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).

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

<table>
<thead>
<tr>
<th>Effect</th>
<th>LLCI</th>
<th>ULCI</th>
<th>I²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omitting Vasigh et al. [41]</td>
<td>-38.619</td>
<td>-68.129</td>
<td>-9.109</td>
</tr>
<tr>
<td>Omitting Routray et al. [42]</td>
<td>-42.331</td>
<td>-71.560</td>
<td>-13.102</td>
</tr>
<tr>
<td>Omitting Pandey et al. [36]</td>
<td>-29.540</td>
<td>-46.207</td>
<td>-12.873</td>
</tr>
<tr>
<td>Omitting Turan et al. [43]</td>
<td>-35.977</td>
<td>-63.942</td>
<td>-8.011</td>
</tr>
<tr>
<td>Omitting Radhakrishnan et al. [34]</td>
<td>-43.946</td>
<td>-71.827</td>
<td>-16.064</td>
</tr>
<tr>
<td>Omitting Erten et al. [32]</td>
<td>-42.550</td>
<td>-71.641</td>
<td>-13.458</td>
</tr>
<tr>
<td>Omitting Vahedi et al. [30]</td>
<td>-43.098</td>
<td>-71.769</td>
<td>-14.428</td>
</tr>
<tr>
<td>Omitting Leung et al. [35]</td>
<td>-38.666</td>
<td>-65.573</td>
<td>-11.758</td>
</tr>
<tr>
<td>Omitting Khan et al. [37]</td>
<td>-40.938</td>
<td>-70.591</td>
<td>-11.285</td>
</tr>
<tr>
<td>Omitting Pandey et al. [38]</td>
<td>-40.353</td>
<td>-70.004</td>
<td>-10.702</td>
</tr>
<tr>
<td>Omitting Ozgencil et al. [39]</td>
<td>-41.482</td>
<td>-70.994</td>
<td>-11.971</td>
</tr>
<tr>
<td>Omitting Khurana et al. [43]</td>
<td>-42.033</td>
<td>-71.355</td>
<td>-12.711</td>
</tr>
</tbody>
</table>

LLCI: lower limit confidence interval; ULCI: upper limit confidence interval.
Figure 4. Influence diagnostics of the included studies
Influence analysis identified Vasigh et al.\cite{41} and Ozgencil et al.\cite{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

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

MD: Mean difference; CI: confidence interval

### Table 5. Mean difference change of VAS after removing outliers

<table>
<thead>
<tr>
<th></th>
<th>MD</th>
<th>95% CI</th>
<th>p</th>
<th>%95 PI</th>
<th>I²</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>-0.85</td>
<td>-1.46; -0.24</td>
<td>0.0131</td>
<td>-2.64; 0.93</td>
<td>89%</td>
<td>79.8; 93.5</td>
</tr>
<tr>
<td>Pandey et al.[36]</td>
<td>-0.59</td>
<td>-0.85; -0.34</td>
<td>0.0013</td>
<td>-1.00; -0.19</td>
<td>38.2%</td>
<td>0; 74</td>
</tr>
</tbody>
</table>

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

### Table 6. Relative risk change of nausea after removing outliers

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>%95 PI</th>
<th>I²</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>0.70</td>
<td>0.51; 0.97</td>
<td>0.0348</td>
<td>0.50; 0.99</td>
<td>0%</td>
<td>0; 60</td>
</tr>
<tr>
<td>Influentials removed*</td>
<td>0.95</td>
<td>0.78; 1.16</td>
<td>0.61</td>
<td>0.60; 1.52</td>
<td>0%</td>
<td>0; 65</td>
</tr>
</tbody>
</table>

*: 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

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>%95 PI</th>
<th>I²</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>0.54</td>
<td>0.34; 0.85</td>
<td>0.0137</td>
<td>0.30; 0.98</td>
<td>0%</td>
<td>0; 65</td>
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<tr>
<td>Influentials removed*</td>
<td>0.67</td>
<td>0.45; 1.00</td>
<td>0.0513</td>
<td>0.33; 1.35</td>
<td>0%</td>
<td>0; 68</td>
</tr>
</tbody>
</table>

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

### Table 8. Relative risk change of sedation after removing outliers

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>%95 PI</th>
<th>I²</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>2.58</td>
<td>1.41; 4.74</td>
<td>0.0069</td>
<td>1.23; 5.42</td>
<td>0%</td>
<td>0; 65</td>
</tr>
<tr>
<td>Influentials removed*</td>
<td>2.38</td>
<td>1.17; 4.84</td>
<td>0.0248</td>
<td>0.69; 8.15</td>
<td>0%</td>
<td>0; 71</td>
</tr>
</tbody>
</table>

*: 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

<table>
<thead>
<tr>
<th></th>
<th>RR</th>
<th>95% CI</th>
<th>p</th>
<th>%95 PI</th>
<th>I²</th>
<th>95% CI</th>
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</thead>
<tbody>
<tr>
<td>Main analysis</td>
<td>0.61</td>
<td>0.20; 1.87</td>
<td>0.2559</td>
<td>0.07; 5.68</td>
<td>25%</td>
<td>0; 71</td>
</tr>
<tr>
<td>Influentials removed*</td>
<td>0.45</td>
<td>0.12; 1.64</td>
<td>0.1170</td>
<td>0.005; 43.4</td>
<td>0%</td>
<td>0; 90</td>
</tr>
</tbody>
</table>

*: Radhakrishnan et al.[34]. RR: Relative risk; CI: Confidence interval; PI: Prediction interval
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 -39.91 mg 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.\textsuperscript{22} However, there are conflicting reports in literature regarding these effects.\textsuperscript{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.\textsuperscript{41} and Samarah et al.\textsuperscript{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.\textsuperscript{41} study was excluded. In the Vasigh et al.\textsuperscript{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.,\textsuperscript{34} 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


Conflict of Interest: No conflict of interest was declared by the authors.

Use of AI for Writing Assistance: ChatGPT 3.5 (OpenAI, 2023) was used for writing assistance.

Financial Disclosure: The authors declared that this study received no financial support.

Peer-disclosure: Externally peer reviewed.

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