Gabapentin prophylaxis for postoperative nausea and vomiting in abdominal surgeries: a quantitative analysis of evidence from randomized controlled clinical trials

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Editor’s key points

- The authors examined the evidence base for the effectiveness of gabapentin in preventing postoperative nausea and vomiting (PONV).
- They found support for the use of preoperative gabapentin in PONV prophylaxis, especially in abdominal surgery.
- Interestingly, the benefits of gabapentin appeared reduced in the presence of the use of propofol.

Introduction. Postoperative nausea and vomiting (PONV) is frequently encountered in the surgical recovery room. Abdominal surgery is one important risk factor for increased incidence of PONV. Gabapentin, an anticonvulsant with known postoperative analgesic properties, has shown some activity against PONV. Results from clinical trials evaluating the anti-emetic efficacy of gabapentin are conflicting. The present meta-analysis was performed to examine this issue.

Methods. Seventeen randomized placebo-controlled trials reporting PONV with preoperative gabapentin administration in patients undergoing abdominal surgery were included for analysis. Outcomes evaluated were nausea, vomiting, composite PONV and the use of rescue anti-emetic medication in the postoperative period.

Results. The pooled relative risk (RR), estimated using the random effects model of the metafor package for R, was 0.76 (95% CI 0.58–0.98) for nausea, 0.62 (0.45–0.85) for vomiting, 0.71 (0.39–1.28) for data represented as composite PONV (possibly biased by a single study, as observed in the sensitivity analysis), and 0.6 (0.41–0.89) for rescue anti-emetic use. There was a significant RR reduction for nausea and vomiting when propofol was not used as induction and/or maintenance for anaesthesia. In the abdominal hysterectomy subgroup, there was a significant RR reduction for vomiting but not for nausea.

Discussion. The present analysis provides evidence supporting preoperative gabapentin as a pharmacotherapy for prevention of PONV in patients undergoing abdominal surgeries. Future studies comparing preoperative gabapentin with 5HT3 antagonists are needed to precisely define its role in PONV.

Keywords: gabapentin; hysterectomy; postoperative nausea and vomiting

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Postoperative nausea and vomiting (PONV) in the surgical recovery room is a common occurrence. Despite being self-limiting, it is associated with substantial distress to patients in the early postoperative period. Its prevention and/or treatment significantly improves patient satisfaction and quality of life.¹ ³ PONV prevention can lead to a substantial reduction in health care costs by reducing the duration of the post-anesthesia care unit (PACU) stay.⁴ ⁵ It is estimated that each episode of emesis delays discharge from the PACU by approximately 20 min.⁶ Furthermore, serious complications, including retinal detachment, aspiration, wound dehiscence, oesophageal rupture, and subcutaneous emphysema, related to PONV can be prevented. The general incidence of PONV ranges from 25% to 30%,⁷ and in some subsets of high-risk patients it can be as high as 80%,⁸ even after preventive pharmacotherapy. The pharmacotherapies used in the prevention/management of PONV include 5-HT3, dopaminergic, histaminic, and NK1 antagonists. Nevertheless, the need for cheaper and more effective therapies cannot be disputed.

Gabapentin, an anticonvulsant, has been shown to be effective as a non-opioid ancillary agent for postoperative pain management.⁹ The safety profile, minimal drug interactions, pharmacokinetics (good oral bioavailability and renal elimination), and relatively flat dose–response relationship with respect to safety and efficacy favour its clinical use.¹⁰ ¹¹ Interestingly, in the recent past, gabapentin’s anti-nausea effects were noted when there was a marked improvement in the chemotherapy-induced nausea in breast cancer patients¹² and subsequently was observed to possess activity against PONV. The exact mechanism for gabapentin’s efficacy in
PONV is not known. While results of a few studies evaluating the efficacy of preoperative gabapentin as a prophylaxis were promising, the results of others did not reach statistical significance and have been equivocal. Hence the present analysis was performed to define the role of gabapentin as a preventive therapy for PONV.

Methods

Randomized placebo-controlled clinical trials comparing preoperative gabapentin administration were identified for evaluation for inclusion in the analyses. The criteria for inclusion were (i) patients undergoing abdominal surgery (open or laparoscopic) under general anaesthesia, (ii) preoperative administration of gabapentin irrespective of dose and timing of the dose with respect to surgery, and (iii) trials reporting nausea, vomiting, postoperative nausea and vomiting, or a proportion of patients requiring rescue anti-emetic medication irrespective of the objective of evaluation were included in the final analysis. Trials evaluating postoperative dosing alone or in addition to preoperative gabapentin were excluded from the final analysis. A literature search using the terms ‘gabapentin’, ‘postoperative nausea and vomiting’, ‘abdominal surgery’, and ‘postoperative pain’ was performed in Medline, Embase and the Cochrane library. Additional studies were identified through cross-references and meta-analyses conducted for evaluation of gabapentin in postoperative pain. All human studies published in full-text or abstract forms were initially screened for inclusion without applying any language restrictions. Titles and abstracts from the electronic search were reviewed. After initial review of the abstracts, the relevant studies were identified and a detailed evaluation of the full text was done. All data with regard to authorship, year of publication, study design, study population (i.e. type of abdominal surgery), baseline patient characteristics, gabapentin dose, type of surgery, type and duration of anaesthesia (when data were not available, the duration of surgery was taken as the duration of anaesthesia), number of patients, and relevant outcomes were extracted from the selected studies. The methodological quality of the included studies was assessed using the Downs and Black score. The whole process was undertaken independently by two authors and all the conflicts were resolved by discussion among all authors.

Outcomes

The outcomes evaluated were postoperative nausea, vomiting, composite of nausea and vomiting (PONV, as some studies had reported a composite outcome of nausea and vomiting), and the proportion of patients requiring rescue anti-emetic medication.

Statistical analyses

Statistical analyses were performed using the metafor package for R. For each individual study the relative risk (RR) was calculated using the reported events of relevant outcomes. Pooled RR for individual outcomes was estimated using the random effects model of the metafor package. Heterogeneity was assessed based on the calculated $I^2$ (the proportion of total variability explained by heterogeneity), estimated using the restricted maximum likelihood–based method. A moderator analysis was performed using the mixed effects modelling approach (incorporating weighted least squares regression for the moderator in the random effects model) to assess the contribution of study level covariates to the overall heterogeneity and their impact on the effect size. Age, percentage of females in each study, postoperative opioid consumption, and duration of anaesthesia were the continuous variables, while surgery type and anaesthetic agent used, dose of gabapentin, and timing of the dose were the categorical variables used as covariates in the mixed effects model. The effect of postoperative opioid consumption was evaluated after computing the standardized mean difference between the placebo and gabapentin groups. To assess the publication bias we plotted the log relative risk vs the standard error of the individual studies. The symmetry of the plot was assessed using Egger’s test. The trim and fill method was used to estimate the number of studies missing from the meta-analysis due to the suppression of the most extreme results on one side of the funnel plot. A Galbraith plot was also plotted to assess the same. A sensitivity analysis was conducted using leave-one-out analysis. Briefly, in this procedure individual studies were excluded from the model and the influence of the exclusion of that study on the model parameters was assessed.

Results

Seventeen studies were included in the final analysis. The literature search and study selection is represented in Fig. 1. The characteristics of the included studies are shown in Table 1. The included studies differed with respect to the type of surgery and the gabapentin dose evaluated. The selected studies contained a total of 1605 patients, with 810 in the gabapentin group and 795 in the placebo group. Eight studies were conducted in patients undergoing hysterectomy, three studies each for open and laparoscopic cholecystectomy patients, and one study each with donor nephrectomy, major bowel surgery, and laparoscopic-assisted reproductive surgery patients. Gabapentin was administered either 1 or 2 h prior to surgery in all the studies. In two studies an additional dose of gabapentin was administered the night before surgery. The data primarily collected from the studies were the study design; gabapentin dose; number of nausea, vomiting, and PONV events; number of rescue anti-emetic events; and also the induction and maintenance agents used for anaesthesia.

Outcomes

Postoperative nausea

Ten studies comprising a total of 632 patients (324 in the gabapentin group and 308 in the placebo group) were included for pooling the RR for postoperative nausea. The pooled RR was 0.76 (95% CI 0.58–0.98). $I^2$ was 5.8% and the test for heterogeneity was not significant ($P=0.36$) (Fig. 2).
Postoperative vomiting

Ten studies comprising a total of 632 patients (324 in the gabapentin group and 308 in the placebo group) were included for pooling the RR for postoperative vomiting. The pooled RR was 0.62 (95% CI 0.45–0.85). $I^2$ was 0% and the test for heterogeneity was not significant ($P=0.5$) (Fig. 3).

PONV

Seven studies comprising a total of 973 patients (487 each in the gabapentin and placebo groups) were included for pooling the RR for postoperative nausea. The pooled RR was 0.71 (95% CI 0.39–1.28). $I^2$ was 94% and the test for heterogeneity was significant ($P<0.0001$) (Fig. 4).

Postoperative use of anti-emetic rescue medication

Seven studies comprising a total of 578 patients (289 each in the gabapentin and placebo groups) were included for pooling the RR for postoperative nausea. The pooled RR was 0.6 (95% CI 0.41–0.89). $I^2$ was 70% and the test for heterogeneity was significant ($P=0.0045$) (Fig. 5).

Moderator analysis

Continuous moderators, such as study level, differences in age, percentage of females, standardized mean difference in opioid consumption, and the duration of anaesthesia, did not influence the outcome measures in the univariate moderator analysis for nausea, vomiting, PONV, and rescue anti-emetic use. The results of the categorical moderators are displayed in Supplementary Figs. 6 and 7. There was a significant reduction in vomiting when gabapentin was used in abdominal hysterectomies. The RR reduction was not statistically significant in the cholecystectomy, nephrectomy, bowel surgery and laparoscopic-assisted reproductive techniques (LART) subgroups. The type of the surgery was not associated with a reduction in RR when nausea was analysed. There was also a significant reduction in the RR of both nausea and vomiting when propofol was not used as an induction or maintenance agent.

Sensitivity analysis and publication bias

The influence diagnostics and leave-one-out analysis of the studies was conducted to assess whether the effect size of
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<th>Durmus et al.17</th>
<th>Frouzanfar et al.18</th>
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<th>Mohammadi et al.20</th>
<th>Pandey et al.21</th>
<th>Pandey et al.22</th>
<th>Pandey et al.23</th>
<th>Sen et al.24</th>
<th>Srivastava et al.25</th>
<th>Tokmaz et al.26</th>
<th>Turan et al.27</th>
<th>Ghafari et al.28</th>
<th>Ghai et al.29</th>
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<td>563.3 (252.8)</td>
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<td>505.9 (82)</td>
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<td>375.8 (83.5)</td>
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<td>2 (13.3)</td>
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<td>5 (16.1)</td>
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<td>9 (36.0)</td>
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gabapentin on the four main parameters, i.e. nausea, vomiting, PONV and rescue anti-emetic use, was influenced by individual studies. The pooled RR for PONV was not significant (0.71 (95% CI 0.39–1.28)), but when the study by Pandey and colleagues21 was excluded, the RR was significant (0.59 (95% CI 0.5–0.7)) and the $I^2$ value for heterogeneity decreased from 94 to 27.2% (Supplementary Table 2). The Galbraith plot showed no evidence of publication bias (Supplementary Figure 8). The Egger’s test for asymmetry of the funnel plot was non-significant ($P=0.27$). The trim and fill method estimated the number of missing studies in the funnel plot as one.

**Discussion**

The quantitative analysis of the collected data showed that preoperative administration of gabapentin in patients undergoing abdominal surgery was associated with a lower incidence of nausea and vomiting. We observed a reduction of 24% for nausea, 38% for vomiting, no significant reduction in the composite PONV (possibly biased by a single study), and a 40% reduction in the rescue anti-emetic use in patients who received preoperative gabapentin. An earlier analysis by Alayed and colleagues15 also showed that there was a reduction in the incidence of postoperative nausea and vomiting. However, the analysis was focussed on only abdominal hysterectomy patients (11 studies). Also, we consider that combining the composite PONV data in the analysis of both nausea and vomiting outcomes as performed in that analysis could possibly result in biased estimates. In the present analysis we included studies on all abdominal surgeries16–32 that evaluated only preoperative gabapentin (even postoperative gabapentin use was included in the earlier analysis). We
additionally performed subgroup analysis to determine the factors that could influence the effect of gabapentin on postoperative nausea and vomiting (which was not performed in the earlier analysis).

Previous studies have shown that the most reliable independent predictors of PONV were female gender, history of PONV or motion sickness, non-smoker, younger age, duration of anaesthesia with volatile anaesthetics, and postoperative opioids. From the extracted data we were able to analyse whether age, female gender, duration of anaesthesia and postoperative opioid use influence the effect of gabapentin on postoperative nausea and vomiting. None of these factors had a significant influence on the effect size of gabapentin’s reduction in nausea and vomiting. The factors that seemed to influence the efficacy of gabapentin in PONV were the type of surgery and the type of anaesthetic agent used for induction and maintenance. The statistically significant reduction of postoperative vomiting observed in the present analysis in the subgroup of patients undergoing abdominal hysterectomy concurs with the earlier findings in the same patient population. However, the imprecise estimates found in the cholecystectomy group do not rule out the anti-emetic efficacy of preoperative gabapentin. The same could explain the statistically non-significant effects in the individual dosage groups. Also, the subgroups had significant heterogeneity, possibly due to the small number of studies in the individual subgroups. Moreover, the dose–response (efficacy) relationship curve of gabapentin is likely to be flat, as observed in epilepsy, saturable absorption being a plausible explanation. Conversely, the adverse events (commonly somnolence and dizziness) may possibly have a relationship with dose. Although it is difficult, based on the present analysis, to recommend a specific dose,
A preoperative dose of 300 or 600 mg can be justified for evaluation in future studies, providing evidence regarding the benefit–risk profile of gabapentin in this clinical setting.

Another interesting finding not previously reported was the differential efficacy of gabapentin with respect to the use of propofol, either as a maintenance or induction agent. In the pooled analysis of subgroup of studies using propofol, the reduction in the nausea and vomiting events with gabapentin was not statistically significant, but was significant when propofol was not used. The anti-emetic properties of propofol\textsuperscript{35} may explain the differential effects of gabapentin, consequently negating the effects of the latter. This suggests a complex interaction between gabapentin and propofol, although synergistic effects between propofol and gabapentin can be expected due to different pharmacological properties, highlighting the need for additional studies. The anti-emetic effects of propofol are short-lived (up to 6 h),\textsuperscript{12} while gabapentin possibly provides long-lasting effects (possibly \textgtr 24 h), as it has been shown to be effective in delayed chemotherapy-induced nausea and vomiting\textsuperscript{12} and has postoperative analgesia even after 24 h\textsuperscript{16}. This precludes making an evaluation on any temporal relationship, as the included studies reported the events occurring only in the first 24 h postoperative period.

The speculated mechanisms of anti-emetic properties of gabapentin include decreased tachykinin neurotransmission,\textsuperscript{12 37–39} decreased calcium influx in area postrema,\textsuperscript{40 41} reduced inflammation at the surgical trauma site,\textsuperscript{42} as inflammation could lead to postoperative ileus and subsequently to PONV,\textsuperscript{43} and reduced anxiety,\textsuperscript{44} apart from the direct effect of decreased opioid consumption (seen with preoperative gabapentin use) on nausea and vomiting. Even though the postoperative opioid consumption is significantly lower with preoperative gabapentin as compared with the placebo group (observed in the previous analysis), we did not observe any influence on the effect size of gabapentin on postoperative nausea and vomiting in the

### Table: Pooled Relative Risk for PONV

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<thead>
<tr>
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<td>Studies</td>
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**RE Model**

![Fig 4. Pooled analysis of composite postoperative nausea and vomiting.](image-url)
moderator analysis. This shows that mechanisms other than the decreased consumption of opioids are possibly responsible for gabapentin's anti-emetic property.

In the sensitivity analysis, the study by Pandey and colleagues\(^\text{21}\) had a significant impact on the results of the PONV endpoint. The pooled RR estimates showed that the effect of gabapentin on the incidence of PONV was not significant \([RR 0.71 (95\% CI \, 0.39–1.28)]\). Exclusion of this study resulted in a statistically significant finding \([RR 0.59 (95\% CI \, 0.5–0.7)]\).

This study by Pandey and colleagues\(^\text{21}\) showed that preoperative gabapentin (300 mg) use caused an increased incidence of PONV (38/153 compared with 8/153 in the placebo group). However, in a study by the same authors in 2006,\(^\text{23}\) it was shown that the preoperative use of gabapentin (600 mg) indeed had a beneficial effect on the incidence of PONV (46/125 compared with 75/125 in the placebo group). Both the studies were done in laparoscopic cholecystectomy patients.

The reasons for this disparity are unknown; we believe that this difference could be due to the fact that PONV was not the primary endpoint in the first study, whereas it was in the second. This could have led to differences in study conduct and analysis. Similarly, concerns about the reliability of the data not formally collected as the primary endpoint were raised in another recent review.\(^\text{45}\)

In the present analysis the observed reduction in postoperative nausea and vomiting with preoperative gabapentin support our recommendation of including gabapentin in the armamentarium of pharmacotherapies for PONV in patients undergoing abdominal surgery. The current treatment guidelines recommend 5-HT\(_3\), dopaminergic, and histaminic antagonists as prophylaxis and treatment for PONV.\(^\text{34}\) Based on the additional analgesic properties, safety profile, and cost, gabapentin might be usefully included in the current list of PONV prophylactic agents.

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**Fig 5** Pooled analysis of postoperative use of rescue medication.
Conclusion

The present analysis overcomes the limitations of earlier analyses and the additional moderator and sensitivity analyses conducted provide strong evidence favouring preoperative gabapentin as a pharmacotherapy for prevention of PONV in patients undergoing abdominal surgeries. The use of propofol in the perioperative period could possibly be an important factor influencing the decision to use gabapentin as a preventative agent. Nevertheless, the analgesic properties and a possible longer duration of action favour preoperative gabapentin use irrespective of the anaesthetic agent. Future studies comparing the efficacy of gabapentin with the more commonly used 5HT3 antagonists are needed to precisely define the role of preoperative gabapentin in PONV.

Supplementary material

Supplementary material is available at British Journal of Anaesthesia online.

Authors’ contributions

S.A., I.S., and S.B. were involved in the data extraction. S.A., I.S., A.S., D.H., and A.C. were involved in the data analysis and the drafting and editing of the manuscript. D.H. and A.C. reviewed and approved the final manuscript.

Declaration of interest

None declared.

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