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Gabapentin for the hemodynamic response to intubation: systematic review and meta-analysis

La gabapentine pour atténuer la réponse hémodynamique à l'intubation: compte rendu méthodique et méta-analyse

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Abstract

Purpose Endotracheal intubation is the gold standard for securing the airway before surgery. Nevertheless, this procedure can produce an activation of the sympathetic nervous system and result in a hemodynamic response which, in high-risk patients, may lead to cardiovascular instability and myocardial ischemia. The aim of this review was to evaluate whether gabapentin can attenuate this response and whether such an attenuation could translate into reduced myocardial ischemia and mortality.

Source We searched MEDLINE®, EMBASE™, CINAHL, AMED, and unpublished clinical trial databases for randomized-controlled trials that compared gabapentin with control, fentanyl, clonidine, or beta blockers for attenuating the hemodynamic response to intubation. Primary outcomes were mortality, myocardial infarction, and myocardial ischemia. Secondary outcomes were hemodynamic changes following intubation.

Principal findings We included 29 randomized trials with only two studies at low risk of bias. No data were provided for the primary outcomes and no studies included high-risk patients. The use of gabapentin resulted in attenuation in the rise in mean arterial blood pressure [mean difference (MD), −12 mmHg; 95% confidence interval (CI), −17 to −8] and heart rate (MD, −8 beats·min⁻¹; 95% CI, −11 to −5) one minute after intubation. Gabapentin also reduced the risk of hypertension or tachycardia requiring treatment (risk ratio, 0.15; 95% CI, 0.05 to 0.48). Data were limited on adverse hemodynamic events such as bradycardia and hypotension.

Conclusion It remains unknown whether gabapentin improves clinically relevant outcomes such as death and myocardial infarction since studies failed to report on these. Nevertheless, gabapentin attenuated increases in heart rate and blood pressure following intubation when compared with the control group. Even so, the studies included in this review were at potential risk of bias. Moreover, they did not include high-risk patients or report adverse hemodynamic outcomes. Future studies are required to address these limitations.

Résumé

Objectif L’intubation endotrachéale constitue l’étoile or de la prise en charge des voies aériennes avant une chirurgie. Toutefois, cette intervention peut entraîner une activation du système nerveux sympathique et provoquer une réponse hémodynamique qui, chez les patients courant un risque élevé, pourrait mener à une instabilité cardiovasculaire et une ischémie myocardique. L’objectif de ce compte rendu était d’examiner si la gabapentine pouvait atténuer cette réponse et si une telle atténuation pouvait se traduire en une réduction de l’ischémie myocardique et de la mortalité.

Source Nous avons effectué des recherches dans les bases de données MEDLINE®, EMBASE™, CINAHL, AMED, ainsi que dans les bases de données d’études cliniques non publiées afin d’en extraire les études randomisées contrôlées comparant la capacité de la gabapentine par rapport à un groupe témoin, au fentanyl, à la clonidine ou à des béta-bloquants, à atténuer la réponse hémodynamique à l’intubation. La mortalité, l’infarctus du myocarde et l’ischémie myocardique étaient les...
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Constatations principales Nous avons inclus 29 études
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faible de biais. Aucune donnée n’était fournie concernant
7
les critères d’évaluation principaux et aucune étude
n’incluait de patients à risque élevé. L’utilisation de la
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batement-min\(^{-1}\); IC 95 %, −11 à −5) une minute après
l’intubation. La gabapentine a également réduit le risque
d’hypertension ou de tachycardie nécessitant un traitement
(risque relatif, 0,15; IC 95 %, 0,05 à 0,48). Les données
concernant les complications hémodynamiques telles que
la bradycardie et l’hypotension étaient limitées.

Conclusion Nous ne savons pas si la gabapentine
améliore des résultats pertinents d’un point de vue
clinique tels que le décès ou l’infarctus du myocarde,
etant donné que les études examinées ne faisaient pas
mention de ces données. Toutefois, la gabapentine a
atténué les augmentations de fréquence cardiaque et de
tension artérielle après l’intubation comparativement au
groupe témoin. Ceci étant dit, les études incluses dans ce
compte rendu couraient un risque potentiel de biais. De
plus, elles n’incluaient pas de patients à risque élevé ni ne
rapportaient de complications hémodynamiques. Des
études supplémentaires sont nécessaires pour pallier ces
limitations.

Endotracheal intubation is the gold standard for securing
the airway before surgery. Nevertheless, this procedure
may cause activation of the sympathetic nervous system
and release of catecholamines, resulting in a hemodynamic
response that precipitates an increase in heart rate (HR) and
blood pressure. This response does not cause problems in
most patients; however, in high-risk patient groups, such as
those with preexisting cardiovascular disease, such
responses may increase the risk of myocardial ischemia,
myocardial infarction, and mortality.\(^1\) As the number of
elderly patients undergoing surgery increases, adverse
cardiovascular responses to endotracheal intubation may
therefore present an increasing problem in the
perioperative period. Many agents have been used to
attenuate this response, but few studies report clinically
relevant outcomes such as morbidity or mortality.\(^2\)

Increases in hemodynamic and sympathetic responses
around the perioperative period may increase myocardial
demand and ensuing adverse cardiac outcomes.\(^3\) Triggers
for these reactions include intubation, extubation, surgery,
and pain. The likelihood of such adverse effects led to the
conduct of randomized-controlled trials evaluating
 cardioprotective agents, such as beta blockers and
clonidine, in reducing perioperative myocardial events.
The Perioperative Ischemic Evaluation (POISE)\(^4\) study
found that perioperative metoprolol reduced myocardial
infarction; however, the study did not focus specifically on
the specified time period of intubation and there was an
increase in overall mortality and stroke. Clonidine has also
shown initial promise,\(^5\) although results of the recent
POISE 2 study showed no reduction in cardiac events or
mortality and an increase in clinically significant
hypotension and non-fatal cardiac arrest.\(^6\) Therefore, the
search for alternative agents that do not produce such
adverse effects is a clinically important issue for high-risk
patients undergoing surgery.

Gabapentin has proven efficacy in reducing
postoperative pain, lowering opioid consumption, and
reducing postoperative nausea and vomiting.\(^7\) A recent
meta-analysis has also identified the benefits of gabapentin
with regard to preoperative anxiety and chronic pain at the
expense of an increase in sedation.\(^8\) Over the last decade,
randomized-controlled trials have been published
indicating that gabapentin may also be useful in
attenuating the hemodynamic response to intubation.\(^9\)
Nevertheless, these studies included a small number of
participants and were not conducted in multiple clinical
populations. Moreover, it is as yet unknown how
gabapentin compares with other agents and whether such
reductions in hemodynamic variables could translate into
reductions in clinically relevant postoperative outcomes.

Due to the disappointing results from clinical trials of
clonidine and beta blockers in reducing perioperative
myocardial events,\(^10\) this review aimed to evaluate
whether gabapentin can attenuate the hemodynamic
response to intubation and whether this can translate into
reductions in myocardial ischemia and myocardial
infarction and ultimately reduce postoperative mortality.

Methods

Search strategy

In conducting this review, we adhered to the standards of
reporting in the Preferred Reporting Items for Systematic
Reviews and Meta-Analyses (PRISMA) checklist.\(^11\) We
prospectively registered the review on the PROSPERO
website using the registration number CRD42015027012.
A deviation from the original protocol was the addition of
intravenous fentanyl as a comparison due to its use as the standard agent at induction of anesthesia. We searched the following databases: MEDLINE® (1946-September 2015) (Appendix), EMBASE™ (1974- September 2015), CINAHL (1981- September 2015), AMED (1985-September 2015), and CENTRAL (until September 2015). We searched for studies using the keywords in the title and abstract, gabapentin, Neurontin, and intubation. The MeSH terms intubation and intratracheal were exploded and combined with the above terms. We also searched for unpublished studies from Clinicaltrials.gov, the ISRCTN registry, and the WHO international clinical trials registry. Furthermore, we searched the reference lists of the identified studies and used Google Scholar to identify studies that had cited those included. We contacted the authors if further information was required.

Inclusion criteria

We included randomized-controlled trials that compared gabapentin with either placebo or no treatment in patients undergoing endotracheal intubation before surgery. We also included studies comparing the administration of gabapentin with fentanyl, clonidine, or beta blockers. We included adult patients only (> 15 yr old) undergoing any type of surgery. There were no restrictions based on publication status or language. When necessary, we used Google Translate to translate papers in non-English-language papers. Two study authors (B.D. and M.S.) independently evaluated the identified studies against the inclusion criteria, and agreement was reached by consensus.

Outcomes

The primary outcomes were mortality, myocardial ischemia, and myocardial infarction. We defined mortality as early (< 48 hr) and late (30 days). If studies reported more than one time point, we included the earliest time in the analysis. Myocardial ischemia was defined as ST segment depression from continuous electrocardiogram (ECG) recordings. Myocardial infarction was defined as two of the following three criteria: chest pain, ECG ischemic changes, and/or > 25% rise in high-sensitivity troponin measurements. Secondary outcomes included HR, mean arterial blood pressure, systolic blood pressure (SBP), and diastolic blood pressure (DBP) measured at one, five, and ten minutes after intubation. We also measured the following outcomes: arrhythmias, plasma catecholamine concentrations, hypotension (requiring treatment), bradycardia (requiring treatment), and tachycardia or hypertension (requiring treatment).

Data extraction and risk of bias

Two study authors (B.D. and M.S.) extracted the following information onto an electronic database: study name, year of publication, mean age of participants, percentage of female participants, sample size, intervention, comparator, country, perioperative medication, induction agents, maintenance agents, laryngoscope and endotracheal tube used, participant population, type of surgery, and duration of intubation. The same two authors assessed risk of bias using the Cochrane tool for assessing risk of bias, and agreement was reached by consensus. We assessed the following domains: randomization, allocation concealment, blinding, attrition bias, selective outcome reporting, and other sources of bias. These domains were assessed as low risk, unclear risk, and high risk and presented in a risk of bias table.

Statistical analysis

We present continuous outcomes using mean difference (MD) and dichotomous outcomes using risk ratios (RR). The precision of outcomes is presented with 95% confidence intervals (95% CI). We regarded a 10% relative risk difference in dichotomous outcomes, a 10 mmHg MD in blood pressure, and 5 beats-min⁻¹ MD in HR as clinically significant. We were unaware of any data directly linking changes in hemodynamic variables and risk of myocardial events, and therefore, these values for clinical significance were not empirically derived. Where data were not presented, authors were contacted to provide further information. If no response was received, the results were extracted from published graphs. If standard deviations were not published, we estimated these from other studies in the meta-analysis. We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group criteria to assess the quality of evidence for each outcome. The evidence is downgraded owing to any concerns regarding the indirectness of evidence, lack of precision in effect estimates, potential publication bias, unexplained heterogeneity, and risk of bias in results. This is a qualitative downgrading from high quality to moderate, low, or very low quality dependent on the concerns cited above. We made no statistical adjustment of results.

Data were aggregated using a random effects model due to substantial clinical heterogeneity in the gabapentin dose and baseline hemodynamic variables of the participants. Statistical heterogeneity is presented using the I² statistic with a corresponding P value derived from the Chi square statistic. We regarded I² of > 50% or P < 0.10 as evidence of statistical heterogeneity. When more than ten studies were included in the meta-analysis, we assessed small
study effects, including possible publication bias, using Egger’s linear regression test.\textsuperscript{15} We regarded a one-tailed $P < 0.10$ as evidence of small study effects.

Investigation of heterogeneity was conducted using a method of moments random-effects meta-regression.\textsuperscript{16} Covariates included the dose of gabapentin and baseline hemodynamic variables of the participants. We calculated the baseline hemodynamic measurements by taking the mean measurement from the gabapentin and control groups recorded before induction of anesthesia (where reported).

We assessed residuals for normality, linearity, and heteroscedasticity. We used Cook’s distance to assess the model for influential cases and the variance inflation factor for evidence of multicollinearity. We present results as the $R^2$ analogue with a corresponding $P$ value for the model (significance level $P < 0.10$). We conducted sensitivity analysis by including studies at low risk of bias (defined as low risk for randomization, allocation concealment, blinding and attrition bias, and no high-risk domains), excluding studies with estimated standard deviations, and using “Remove-One” analysis.

We conducted trial sequential analysis for each outcome when gabapentin was compared with control. This analysis allows for control of type I errors, which may occur early on in the systematic review process (false discovery rate). This is analogous to the problems of multiple statistical testing in primary studies. Monitoring boundaries can be constructed so that, early in the evidence accrual, a greater $Z$ score is required to reach statistical significance. As each study is published, a cumulative $Z$ score is calculated, and if this crosses the monitoring boundary, it can be assumed that statistical significance is adjusted for multiple comparisons. We constructed O'Brien-Fleming monitoring boundaries for benefit assuming an alpha level of 0.05 and a 1-beta of 0.80. In addition, we calculated the required number of included participants to provide a definitive result (information size) in order to reduce type II errors.\textsuperscript{17} This part of the analysis is analogous to a sample size calculation in primary research studies, which also makes allowances for the statistical heterogeneity of results and the uncertainty that surrounds these. We used previously stated clinically relevant MDs for continuous outcomes (10 mmHg or 5 beats-min$^{-1}$) and 20\% or 50\% relative risk reductions for dichotomous outcomes. We used the included studies in each analysis to estimate the diversity ($D^2$ with a calculated heterogeneity correction) and variance. We conducted sensitivity analyses around these estimates. All analyses were performed using Review Manager 5.3,\textsuperscript{18} Comprehensive Meta-Analysis V3.3,\textsuperscript{19} and Trial Sequential Analysis 0.9 beta software from the Copenhagen Trial Unit (http://www.ctu.dk/tsa).

Results

Description of included studies

We screened 95 studies identified from searching electronic databases and handsearching reference lists (Fig. 1) and included 29 studies in the meta-analysis (Table).\textsuperscript{20-48} All the included studies enrolled American Society of Anesthesiologists physical status I or II patients with no preexisting cardiac risk factors, and there were no

Fig. 1 PRISMA flowchart for included studies

20 studies from MEDLINE
45 studies from EMBASE
1 study from Cinahl
0 studies from AMED
21 studies from CENTRAL

95 studies underwent screening

65 studies excluded

30 studies underwent full text review

1 study excluded as publication was unavailable

29 studies included in the meta-analysis

7 studies identified from searching of references and citations
1 unpublished study from clinical trial databases

Author Proof
<p>| Study name          | Mean age | Female (%) | n     | Intervention                                      | Comparator                                      | Country | Perioperative medication                                      |
|---------------------|----------|------------|-------|--------------------------------------------------|------------------------------------------------|
| Abdel-Halim et al. 2009 | 46.3     | 100%       | 80    | 800 mg gabapentin 1 hr before surgery            | 1) No medication 2) 16 mg dexamethasone         | Egypt   | Patients with anxiety received midazolam (2-4 mg)           |
| Aggarwal, Badani and Jain 2015 | 36.6     | 83%        | 90    | 1) 300 mg gabapentin night before and day of surgery 2) 300 mg gabapentin night before and 600 mg day of surgery | Placebo                                        | India   | Pethidine (1 mg·kg⁻¹) and promethazine                    |
| Ali et al. 2009     | 29.5     | 46%        | 50    | 1,200 mg gabapentin 2 hr before surgery          | Placebo                                        | Egypt   | None                                                        |
| Ali, Elnakera and Samir 2013 | 31.6     | 50%        | 60    | 1) 800 mg gabapentin 2 hr before surgery 2) 1,200 mg gabapentin 2 hr before surgery | Placebo                                        | Egypt   | None                                                        |
| Ayatollahi et al. 2014 | NR       | NR         | 30    | 100 mg gabapentin night before and 800 mg 90 min before surgery | Placebo                                        | Iran    | None                                                        |
| Bafna, Goyal and Garg 2011 | 39.7     | 76%        | 90    | 1) 600 mg gabapentin 1 hr before surgery 2) 1,000 mg gabapentin 1 hr before surgery | Placebo                                        | India   | Midazolam (0.05 mg·kg⁻¹) and glycopyrrolate (0.004 mg·kg⁻¹) |
| Bala, Bharti and Ramesh 2015 | 54.6     | 68%        | 100   | 1) 800 mg gabapentin 2 hr before induction 2) 800 mg night before and 2 hr before induction | Placebo                                        | India   | NR                                                          |
| Bhandari and Shahi 2013 | 42.6     | NR         | 40    | 900 mg gabapentin 2 hr before induction          | Placebo                                        | India   | Ondansetron (0.1 mg·kg⁻¹)                                  |
| Bhandari et al. 2014 | 42.9     | 66%        | 40    | 600 mg gabapentin 2 hr before surgery            | Placebo                                        | India   | None                                                        |
| Bharti et al. 2013  | 46.5     | 100%       | 40    | 600 mg gabapentin 2 hr before surgery            | Placebo                                        | India   | None                                                        |
| Farzi et al. 2015   | 27.6     | 85%        | 103   | 900 mg gabapentin 2 hr before surgery            | Placebo                                        | Iran    | None                                                        |
| Fassoulaki et al. 2006 | 42       | 100%       | 44    | 400 mg gabapentin TID day before surgery and 6am on the day of surgery | Placebo                                        | Greece  | Metoclopramide (10 mg)                                    |
| Iftikhar et al. 2011 | 36.5     | 40%        | 60    | 800 mg gabapentin 1 hr before surgery            | Placebo                                        | Pakistan| None                                                        |
| Kaya et al. 2008    | 43.5     | 53%        | 60    | 800 mg gabapentin 2 hr before surgery            | Placebo                                        | Turkey  | Midazolam (0.03 mg·kg⁻¹)                                  |
| Kiran and Verma 2008 | 33.8     | 54%        | 100   | 800 mg gabapentin night before and morning of surgery | Placebo                                        | India   | Alprazolam (0.25 mg)                                     |
| Koç, Memis and Sut 2007 | 38.5     | 0%         | 80    | 800 mg gabapentin 1 hr before surgery            | 1) Placebo 2) 8 mg dexamethasone               | Turkey  | None                                                        |
| Kumari and Pathania 2009 | 30.7     | 49%        | 78    | 900 mg gabapentin 2 hr before induction          | Placebo                                        | India   | Glycopyrrolate (0.2 mg) and ondansetron (4 mg)             |
| Marashi, Ghafari and Salimnia 2009 | 32.8     | 51%        | 75    | 900 mg gabapentin 2 hr before surgery            | 1) Placebo 2) 200 µg clonidine                 | Iran    | Midazolam (0.03 mg·kg⁻¹)                                  |
| Memiş et al. 2006   | 44.6     | 42%        | 89    | 1) 400 mg gabapentin 1 hr before surgery 2) 800 mg gabapentin 1 hr before surgery | Placebo                                        | Turkey  | None                                                        |
| Montazeri et al. 2011 | 38       | 45%        | 96    | 800 mg gabapentin 90 min before surgery          | 1) Placebo 2) 0.3 mg clonidine                 | Iran    | None                                                        |
| Neogi et al. 2012   | 40.4     | 63%        | 60    | 900 mg gabapentin 2 hr before induction          | Vitamin B                                     | India   | None                                                        |</p>
<table>
<thead>
<tr>
<th>Study name</th>
<th>Mean age</th>
<th>Female (%)</th>
<th>n</th>
<th>Intervention</th>
<th>Comparator</th>
<th>Country</th>
<th>Perioperative medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parida et al. 2015</td>
<td>37.9</td>
<td>58%</td>
<td>50</td>
<td>800 mg gabapentin 2 hr before surgery</td>
<td>1) Placebo 2) fentanyl</td>
<td>India</td>
<td>Diazepam (0.2 mg·kg⁻¹), omeprazole (20 mg) and metoclopramide (10 mg)</td>
</tr>
<tr>
<td>Sanabria Siacara and Pena 2013</td>
<td>31.5</td>
<td>37%</td>
<td>600</td>
<td>800 mg gabapentin 1 hr before surgery</td>
<td>Clonidine 2 µg·kg⁻¹</td>
<td>Mexico</td>
<td>Midazolam (0.02 mg·kg⁻¹)</td>
</tr>
<tr>
<td>Sharma et al. 2012</td>
<td>37.6</td>
<td>NR</td>
<td>120</td>
<td>800 mg gabapentin 1 hr before induction</td>
<td>1) Placebo 2) 300 µg clonidine 3) 400 mg gabapentin and 150 µg clonidine</td>
<td>Kashmir</td>
<td>Metoclopramide (10 mg)</td>
</tr>
<tr>
<td>Shreedhara et al. 2014</td>
<td>40.4</td>
<td>48%</td>
<td>90</td>
<td>900 mg gabapentin 2 hr before surgery</td>
<td>1) Placebo 2) 200 µg clonidine</td>
<td>India</td>
<td>Glycopyrrolate (4 µg·kg⁻¹), ranitidine (1 mg·kg⁻¹) and ondansetron (0.08 mg·kg⁻¹)</td>
</tr>
<tr>
<td>Shrestha, Marhatta and Amatya 2009</td>
<td>33.8</td>
<td>NR</td>
<td>72</td>
<td>1,200 mg gabapentin 2 hr before induction</td>
<td>1) Placebo 2) esmolol</td>
<td>Nepal</td>
<td>None</td>
</tr>
<tr>
<td>Singhal, Kaur and Arora 2015</td>
<td>32.8</td>
<td>63%</td>
<td>100</td>
<td>900 mg gabapentin 90 min before surgery</td>
<td>Clonidine 200 µg</td>
<td>India</td>
<td>None</td>
</tr>
<tr>
<td>Soltanzadeh et al. 2012</td>
<td>28.4</td>
<td>50%</td>
<td>90</td>
<td>900 mg gabapentin 2 hr before surgery</td>
<td>Placebo</td>
<td>Iran</td>
<td>Midazolam (0.05 mg·kg⁻¹)</td>
</tr>
<tr>
<td>Zia et al. 2012</td>
<td>36.7</td>
<td>40%</td>
<td>110</td>
<td>800 mg gabapentin 2 hr before surgery</td>
<td>Placebo</td>
<td>Pakistan</td>
<td>None</td>
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<table>
<thead>
<tr>
<th>Study name</th>
<th>Anesthetic and muscle relaxant</th>
<th>Maintenance</th>
<th>Laryngoscope and tube</th>
<th>Participant population</th>
<th>Type of surgery</th>
<th>Duration of intubation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdel-Halim et al. 2009</td>
<td>Fentanyl (1.5-2 µg·kg⁻¹), thiopentone (3-7 mg·kg⁻¹) and atracurium (5 mg·kg⁻¹)</td>
<td>Isoflurane</td>
<td>NR</td>
<td>ASA I and II, aged 18-65 yr, excluded patients with hypertension and cardiac disease</td>
<td>Mastectomy</td>
<td>NR</td>
</tr>
<tr>
<td>Aggarwal, Baduni and Jain 2015</td>
<td>Thiopentone and vecuronium</td>
<td>Nitrous oxide</td>
<td>Macintosh 3 and 7 mm or 8 mm endotracheal tube</td>
<td>ASA I and II, aged 18-45 yr</td>
<td>Laparoscopic cholecystectomy</td>
<td>NR</td>
</tr>
<tr>
<td>Ali et al. 2009</td>
<td>Propofol (2 mg·kg⁻¹) and vecuronium (0.08 mg·kg⁻¹)</td>
<td>Sevoflurane and nitrous oxide</td>
<td>Macintosh 3 and 7 mm or 8 mm endotracheal tube</td>
<td>ASA I, aged 20-40 yr, normotensive, excluded those with cardiovascular disease</td>
<td>Elective surgery (hemioplasty, arthroscopy, cholecystectomy and vitrectomy)</td>
<td>Patients excluded if longer than 15 sec</td>
</tr>
<tr>
<td>Ali, Elnakera and Samir 2013</td>
<td>Fentanyl (2 µg·kg⁻¹), propofol (2 mg·kg⁻¹) and cisatracurium (0.15 mg·kg⁻¹)</td>
<td>Isoflurane</td>
<td>NR</td>
<td>ASA I and II, 18-60 yr, excluded patients with hypertension</td>
<td>Elective cataract surgery</td>
<td>Patients excluded if more than one attempt</td>
</tr>
<tr>
<td>Study name</td>
<td>Anesthetic and muscle relaxant</td>
<td>Maintenance</td>
<td>Laryngoscope and tube</td>
<td>Participant population</td>
<td>Type of surgery</td>
<td>Duration of intubation</td>
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<tr>
<td>Ayatollahi et al. 2014</td>
<td>Fentanyl (1.5 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
<td>Fixed laryngoscope and 5-5.5 mm endotracheal tube</td>
<td>ASA I and II, aged 30-70 yr</td>
<td>Microlaryngeal surgery</td>
<td>NR</td>
</tr>
<tr>
<td>Bafna, Goyal and Garg 2011</td>
<td>Fentanyl (1 μg·kg⁻¹), thiopentone (5 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>Isoflurane, nitrous oxide and atracurium</td>
<td>Appropriately sized endotracheal tube</td>
<td>ASA I and II, aged 20-60 yr, normotensive, excluded those with cardiovascular disease and hypertension</td>
<td>Elective surgery</td>
<td>Patients excluded if longer than 30 sec or more than one attempt</td>
</tr>
<tr>
<td>Bala, Bharti and Ramesh 2015</td>
<td>Thiopentone (5 mg·kg⁻¹), fentanyl (2 μg·kg⁻¹) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
<td>NR</td>
<td>Hypertensive patients, aged 35-60 yr</td>
<td>Elective surgery</td>
<td>Patients excluded if longer than 30 sec or more than one attempt</td>
</tr>
<tr>
<td>Bhandari and Shahi 2013</td>
<td>Tramadol (2 mg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Halothane and nitrous oxide</td>
<td>NR</td>
<td>ASA I, aged 16-60 yr, excluded patients on anti-hypertensives</td>
<td>Elective surgery</td>
<td>Patients excluded if longer than 30 sec or more than one attempt</td>
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<td>Fentanyl (3 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (800 μg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
<td>NR</td>
<td>ASA I and II, aged 18-60 yr, excluded patients on anti-hypertensives</td>
<td>Laparoscopic cholecystectomy</td>
<td>Patients excluded if more than one attempt</td>
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<td>Bharti et al. 2013</td>
<td>Fentanyl (2 μg·kg⁻¹), propofol (20 mg boluses to BIS target of 60) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Propofol and nitrous oxide</td>
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<td>Propofol (2.25 mg·kg⁻¹), fentanyl (2 μg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
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<td>ASA I and II, aged 18-45 yr</td>
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<td>Propofol (2.5 mg·kg⁻¹) and cisatracurium (0.15 mg·kg⁻¹)</td>
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<td>Maintenance</td>
<td>Participant population</td>
<td>Type of surgery</td>
<td>Duration of intubation</td>
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<td>Ifitkhar et al. 2011</td>
<td>Nalbuphine (0.1 mg·kg⁻¹), thiopentone (5 mg·kg⁻¹) and rocuronium (0.6 mg·kg⁻¹)</td>
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<td>ASA I and II, excluded patients with hypertension, ischemic heart disease and extremes of age</td>
<td>Elective surgery</td>
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<td>Kaya et al. 2008</td>
<td>Fentanyl (2 µg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Sevoflurane and 50% nitrous oxide</td>
<td>Normotensive, ASA I and II</td>
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<td>Kiran and Verma 2008</td>
<td>Propofol (2.5 mg·kg⁻¹) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Halothane and nitrous oxide</td>
<td>ASA I and II, aged 20-50 yr, excluded patients with hypertension</td>
<td>Elective surgery</td>
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<td>Koç, Memiş and Sut 2007</td>
<td>Remifentanil (0.5 µg·kg⁻¹·min⁻¹), propofol (2 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>Propofol, remifentanil and nitrous oxide</td>
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<td>Varicocele surgery</td>
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<td>Kumari and Pathania 2009</td>
<td>Tramadol (100 mg), propofol (2 mg·kg⁻¹) and vecuronium (0.9 mg·kg⁻¹)</td>
<td>Propofol and nitrous oxide</td>
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<td>Elective surgery</td>
<td>Patients excluded if longer than 30 sec or more than one attempt</td>
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<td>Marashi, Ghafari and Saliminia 2009</td>
<td>Fentanyl (2.5 µg·kg⁻¹), thiopental sodium (0.5 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>NR</td>
<td>ASA I and II, aged &lt;45 yr, excluded patients with hypertension and cardiovascular disease</td>
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<td>Memiş et al. 2006</td>
<td>Propofol (2 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>Sevoflurane and nitrous oxide</td>
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<td>Elective surgery</td>
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<td>Montazeri et al. 2011</td>
<td>Fentanyl (3 µg·kg⁻¹), thiopental (5 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>Propofol and nitrous oxide</td>
<td>ASA I and II, aged 18-65 yr, excluded patients with hypertension or cardiovascular disease</td>
<td>Elective surgery</td>
<td>Patients excluded if longer than 15 sec</td>
<td></td>
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<td>Laryngoscope and tube</td>
<td>Participant population</td>
<td>Type of surgery</td>
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<td>Fentanyl (2 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and rocuronium (0.7 mg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
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<td>ASA I and II, aged 18-65 yr, excluded patients with hypertension and cardiac dysfunction</td>
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<td>Parida et al. 2015</td>
<td>Fentanyl (2 μg·kg⁻¹), thiopentone (5 mg·kg⁻¹), vecuronium (0.1 mg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
<td>Macintosh</td>
<td>ASA I, aged 20-50 yr, elective non-cardiac surgery</td>
<td>Elective non-cardiac surgery</td>
<td>Patients excluded if longer than 30 sec</td>
</tr>
<tr>
<td>Sanabria Siacara and Pena 2013</td>
<td>Fentanyl (3 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (100 μg·kg⁻¹)</td>
<td>Sevoflurane and fentanyl</td>
<td>NR</td>
<td>ASA I and II, aged 18-50 yr, excluded patients with hypertension, cardiac disease or on anti-hypertensives</td>
<td>Elective surgery</td>
<td>NR</td>
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<td>Shama et al. 2012</td>
<td>Propofol (2.5 mg·kg⁻¹) and rocuronium (0.9 mg·kg⁻¹)</td>
<td>Isoflurane/halothane and nitrous oxide</td>
<td>NR</td>
<td>ASA I and II, aged 20-60 yr, excluded patients on anti-hypertensives</td>
<td>Elective surgery</td>
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<td>Shreehara et al. 2014</td>
<td>Propofol (2 mg·kg⁻¹) and suxamethonium (2 mg·kg⁻¹)</td>
<td>Isoflurane and nitrous oxide</td>
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<td>ASA I and II, aged 18-60 yr</td>
<td>Elective surgery</td>
<td>NR</td>
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<td>Shrestha, Marhatta and Amatya 2009</td>
<td>Pethidine (0.75 mg·kg⁻¹), propofol (2-2.5 mg·kg⁻¹) and vecuronium (0.1 mg·kg⁻¹)</td>
<td>Halothane</td>
<td>NR</td>
<td>ASA I and II, aged &lt;65 yr, patients with cardiopulmonary disease excluded</td>
<td>Elective surgery</td>
<td>Patients excluded if longer than 30 sec or more than one attempt</td>
</tr>
<tr>
<td>Singhal, Kaur and Arora 2014</td>
<td>Thiopentone (5 mg·kg⁻¹) and succinylcholine (2 mg·kg⁻¹)</td>
<td>Halothane and nitrous oxide</td>
<td>7-8 mm endotracheal tube</td>
<td>ASA I and II, aged 20-50 yr, excluded patients with hypertension</td>
<td>Elective surgery</td>
<td>NR</td>
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<tr>
<td>Soltanzadeh et al. 2012</td>
<td>Fentanyl (2 μg·kg⁻¹), thiopental (5 mg·kg⁻¹) and atracurium (0.5 mg·kg⁻¹)</td>
<td>NR</td>
<td>Macintosh 3 and 7.5-8 mm endotracheal tube</td>
<td>ASA I and II, aged 15-50 yr, excluded patients with hypertension and ischemic heart disease</td>
<td>Elective surgery</td>
<td>Patients excluded if more than one attempt</td>
</tr>
</tbody>
</table>
studies involving patients at high risk for adverse cardiac outcomes. One study included patients with hypertensive disease, and one study used invasive blood pressure monitoring to record hemodynamic variables. Only one study provided details of the equipment used to measure noninvasive blood pressure. There was clinical heterogeneity in the doses of gabapentin used, with doses ranging from 300-1,200 mg. Most studies administered gabapentin from one to two hours before surgery. In terms of risk of bias assessments, allocation concealment was rarely adequately reported. The risk of bias for each included study is presented in Fig. 2. Only two studies were at low risk of bias. None of the hemodynamic values measured declined below post-induction values following intubation.

Gabapentin vs control

Primary outcomes

None of the included studies reported mortality or myocardial infarction or measured them as outcomes. Nine studies reported myocardial ischemia. There were no events in either group in any of the included studies. All studies reporting myocardial ischemia derived data from ST changes on ECG recordings during the intraoperative period.

Secondary outcomes

Mean arterial blood pressure  Gabapentin attenuated the rise in mean arterial pressure (MAP) at one minute when compared with the control group (MD, −12 mmHg; 95% CI, −17 to −8; low quality) (Fig. 3). At five minutes, the analysis included 21 studies with 1,350 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −9 mmHg; 95% CI, −13 to −5; low quality). At ten minutes, the analysis included 18 studies with 1,244 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −8 mmHg; 95% CI, −11 to −5; low quality). There was evidence of statistical heterogeneity for all time points ($I^2 = 82-93\%$; $P < 0.001$). There was no evidence of small study effects at one or ten minutes ($P = 0.14$ and $P = 0.36$, respectively). There was evidence of small study effects at five minutes ($P = 0.001$); however, the studies were missing from the left of the plot, suggesting a bias against gabapentin for this outcome. On meta-regression analysis, increasing the gabapentin dose or baseline MAP did not significantly predict gabapentin effect at any time point. Trial sequential analysis showed
Gabapentin attenuated the rise in HR at one minute after intubation when compared with the control group (MD, −8 beats·min⁻¹; 95% CI, −11 to −5; moderate quality). At five minutes, the analysis included 25 studies with 1,564 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −6 beats·min⁻¹; 95% CI, −8 to −4; moderate quality). At ten minutes, the analysis included 22 studies with 1,458 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −5 beats·min⁻¹; 95% CI, −7 to −3; moderate quality) (Fig. 4).

There was evidence of statistical heterogeneity at all time points (I² = 46-76%; P < 0.01). There was evidence of small study effects at one and five minutes (P = 0.05 and P = 0.004, respectively); however, the missing studies were to the left of the mean, suggesting a bias against gabapentin. On meta-regression analysis, an increase in the gabapentin dose predicted greater attenuation in HR at one minute (R² = 35%; P = 0.006), five minutes (R² = 38%; P = 0.02), and ten minutes (R² = 52%; P = 0.004). Baseline HR was not a significant predictor at any time point. Trial sequential analysis showed that gabapentin crossed the O’Brien-Fleming boundary for benefit at all time points. In addition, the results for five and ten minutes reached the required information size (1,339 and 784 participants, respectively). Nevertheless, the results for one minute failed to reach the required information size (2,022 participants).

Systolic blood pressure At one minute after intubation, the analysis included 15 studies with 928 participants where the aggregated effect estimate showed gabapentin attenuated the rise in SBP when compared with the control group (MD, −16 mmHg; 95% CI, −22 to −9; low quality). At five minutes, the analysis included 15 studies with 921 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −10 mmHg; 95% CI, −16 to −4; low quality). At ten minutes, the analysis included 13 studies with 855 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −9 mmHg; 95% CI, −16 to −2; low quality).

There was evidence of substantial statistical heterogeneity at all time points (I² = 89-94%; P < 0.001). There was no evidence of small study effects at one (P = 0.27), five (P = 0.43), or ten minutes (P = 0.30). On meta-regression analysis, gabapentin dose and baseline SBP did not significantly predict gabapentin effect. Trial sequential analysis showed that gabapentin crossed the O’Brien-Fleming boundary for benefit at one and five minutes.

**Fig. 2** Risk of bias for included studies. Green indicates low risk, yellow indicates unclear risk, and red indicates high risk.
minutes. Nevertheless, the result for ten minutes did not cross the boundary for benefit. In addition, results at one, five, and ten minutes did not reach the required information size (1,507, 1,163, and 1,654 participants, respectively).

Diastolic blood pressure At one minute after intubation, the analysis included 14 studies with 892 participants where the aggregated effect estimate showed an attenuated rise in DBP with gabapentin when compared with control (MD, −11 mmHg; 95% CI, −15 to −7; low quality). At five minutes, the analysis included 14 studies with 885 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −7 mmHg; 95% CI, −11 to −4; low quality). At ten minutes, the analysis included 13 studies with 855 participants where the aggregated effect estimate showed an attenuated rise with gabapentin (MD, −6 mmHg; 95% CI, −10 to −2; low quality).

There was evidence of substantial statistical heterogeneity at all time points ($I^2 = 79-89\%$; $P < 0.001$). There was no evidence of small study effects at one ($P = 0.32$), five ($P = 0.24$), or ten minutes ($P = 0.30$). On meta-regression analysis, gabapentin dose and baseline DBP did not significantly predict gabapentin effect at any time point. Trial sequential analysis showed that the results for gabapentin crossed the O'Brien-Fleming boundary for

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Gabapentin Mean</th>
<th>SD</th>
<th>Total</th>
<th>Control Mean</th>
<th>SD</th>
<th>Total</th>
<th>Weight</th>
<th>Mean Difference, IV, Random, 95% CI</th>
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<td>Abdel-Halim and colleagues 2009</td>
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Total (95% CI) 792 679 100.00 -8.42 [-11.36, -5.47]
Gabapentin for intubation

benefit for all time points. In addition, the required information size was reached for one, five, and ten minutes (647, 446, and 540 participants, respectively).

Other secondary outcomes

Eight studies\textsuperscript{21,22,25,26,33,35,38,41} reported arrhythmias as an outcome; there were no events in any of the included studies. In terms of catecholamine secretion, one study\textsuperscript{22} concluded that gabapentin resulted in lower secretion of adrenaline one minute after intubation when compared with placebo (MD, $-5$ pg·mL$^{-1}$; 95% CI, $-9$ to $-1$). Nevertheless, the secretion of noradrenaline\textsuperscript{22} was higher when compared with placebo one minute after intubation (MD, 65 pg·mL$^{-1}$; 95% CI, 47 to 83).

Gabapentin use reduced the incidence of hypertension or tachycardia requiring treatment in five studies (RR, 0.15; 95% CI, 0.05 to 0.48; moderate quality). Trial sequential analysis showed that gabapentin crossed the boundary for benefit, although it did not reach the required information size (558 participants). Definitions for this outcome were as follows: SBP $>200$ mmHg or $>30\%$ increase from baseline for more than 60 sec\textsuperscript{22,38} (HR $>130$ beats·min$^{-1}$, SBP $>200$ mmHg or $>30\%$ increase from baseline for more than 60 sec\textsuperscript{26} MAP or HR $>20\%$ of baseline,\textsuperscript{29} MAP $>110$ mmHg\textsuperscript{40}.

One study\textsuperscript{26} conducted in hypertensive patients reported any incidences of hypotension requiring treatment (SBP $<90$ mmHg or $>30\%$ from baseline lasting more than 60 sec); there were no significant differences between the groups (RR, 2.40; 95% CI, 0.74 to 7.79). One study\textsuperscript{31} reported any incidence of bradycardia requiring treatment (HR $<40$ beats·min$^{-1}$). There was no significant difference in bradycardia with gabapentin (RR, 3.00; 95% CI, 0.13 to 69.87).

Gabapentin vs fentanyl, clonidine, or beta blockers

When compared with clonidine, the only significant difference in hemodynamic variables was a higher HR at ten minutes in the gabapentin group when compared with the clonidine group\textsuperscript{37,39,42-44} (MD, 5 beats·min$^{-1}$; 95% CI, 3 to 7; moderate quality). One study\textsuperscript{45} compared gabapentin with a beta blocker (esmolol). The only difference in hemodynamic variables was a higher HR at one minute in the gabapentin group when compared with the esmolol group (MD, 13 beats·min$^{-1}$; 95% CI, 4 to 21).

The incidence of bradycardia was not significantly different when gabapentin was compared with clonidine (RR, 0.49; 95% CI, 0.07 to 3.60) or esmolol (RR, 0.33; 95% CI, 0.01 to 7.68).

One study compared gabapentin with intravenous fentanyl\textsuperscript{41}. Intravenous fentanyl resulted in greater attenuation of HR at one (MD, 14 beats·min$^{-1}$; 95% CI, 8 to 20), five (MD, 12 beats·min$^{-1}$; 95% CI, 7 to 17), and ten minutes (MD, 10 beats·min$^{-1}$; 95% CI, 5 to 15). Furthermore, intravenous fentanyl resulted in greater attenuation of MAP at one minute (MD, 13 mmHg; 95% CI, 8 to 18).

Sensitivity analysis

Only two of the included studies were at low risk of bias\textsuperscript{35,41} which resulted in no significant reductions for many outcomes. Excluding studies with estimated standard deviations did not significantly affect results. “Remove-One” sensitivity analysis showed that there were no influential studies in any of the analyses.

Discussion

There are several limitations with the results of this review. We were unable to provide any results for the primary outcomes because the inclusion of low-risk patients resulted in either zero incidences of these events or lack of reporting of these outcomes within the included studies. Secondly, as previously discussed, there is limited evidence with regard to clinically important adverse events such as hypotension and bradycardia. Many studies were at potential risk of bias, particularly for allocation concealment, which may bias the results from this review\textsuperscript{49}. Indeed, only two studies\textsuperscript{35,41} included in the review were deemed to be at low risk of bias for most domains, which limited the quality of the evidence.\textsuperscript{14} In addition to these issues with internal validity, many of the studies included in the review were conducted in the Middle East and Asia, and therefore, the applicability of our results to North American and European populations is unclear.

With regard to outcome measurements, very few of the included studies provided details of the equipment used to obtain noninvasive blood pressure measurements. As values from oscillometric methods are algorithmically derived, these may vary between devices, which may introduce heterogeneity into our results. Also, this lack of information meant that it was problematic to evaluate whether such devices are valid, precise, and accurate. As the majority of the included studies measured blood pressure at discrete time points, important hypotensive or hypertensive episodes may have been missed, as such discrete measurements may not reflect the average values occurring between such measurements. Finally, it is unclear how gabapentin compares with other standard agents such as lidocaine. Importantly, when gabapentin was directly compared with a standard agent such as...
in high-risk patients, gabapentin was inferior for many hemodynamic outcomes.

Despite the limitations of the review, we found that gabapentin resulted in significant attenuation of mean arterial blood pressure, HR, SBP, and DBP when compared with control (moderate- to low-quality evidence). Most of these results crossed the monitoring boundaries for benefit and reached the required information sizes for a definitive answer on trial sequential analysis, reducing type I and II errors in our analysis. In addition, gabapentin resulted in a significant reduction in the proportion of patients requiring treatment for hypertension or tachycardia. Following intubation, one study found that gabapentin reduced circulating levels of adrenaline and increased noradrenaline. Although data were limited, gabapentin appears comparable with clonidine and beta blockers in terms of its hemodynamic effects following intubation. Increases in gabapentin dosages were associated with greater attenuation of HR responses on meta-regression analysis. Although many of these outcomes reached our predefined clinical thresholds, caution is advised as these were not empirically derived.

The hemodynamic response to intubation involves a stress response, which leads to increases in catecholamine levels and subsequent increases in HR and blood pressure. In high-risk patients, such increases can lead to myocardial ischemia and therefore myocardial infarction. Many agents have been used to attenuate the hemodynamic response to intubation and thus aim to reduce myocardial ischemia. Although agents such as clonidine and beta blockers have shown promise in reducing perioperative cardiac events, the large randomized-controlled POISE studies showed an increase in mortality and stroke with perioperative beta blocker therapy and increases in clinically important hypotension and non-fatal cardiac arrest with clonidine. Therefore, the search continues for effective agents that can reduce perioperative myocardial events in high-risk patients without increasing such adverse events as hypotension and bradycardia and therefore all-cause mortality. Although such perioperative events as intubation, extubation, surgery, and pain can contribute to increasing myocardial demand, our review focused only on the brief hemodynamic response following intubation. Therefore, we advise caution in extrapolating these results with any direct link with longer-term adverse cardiac events in the perioperative period, such as those studied in POISE. Despite this limitation, gabapentin is known to reduce postoperative pain, attenuate the hemodynamic response to intubation, and reduce catecholamine and cortisol responses postoperatively; therefore, longer-term effects on reducing myocardial demand cannot be ruled out.

Gabapentin has proven efficacy as a perioperative analgesic with reductions in pain scores and lower opioid consumption in various types of surgery. Other beneficial effects include reductions in preoperative anxiety, vomiting, and pruritus, with some evidence of reductions in chronic post-surgical pain at the expense of increased sedation. Interestingly, these trials provide the only evidence of the effects of gabapentin in high-risk patients. Within these postoperative pain trials, the results of studies with cardiothoracic surgery patients (which included high-risk cardiac patients) suggest a reduction in postoperative arrhythmia with the use of gabapentin (RR, 0.55; 95% CI, 0.28 to 1.08).

Our review suggests that gabapentin may also be an effective agent for attenuation of the hemodynamic response to intubation. We found only one study suggesting that this might be mediated by reductions in adrenaline when compared with control. Previous in vitro research has suggested that gabapentin may inhibit the release of catecholamines from adrenal chromaffin cells, which may confirm this as a possible mechanism of action. Furthermore, a recent randomized-controlled trial has shown that preoperative gabapentin can reduce postoperative catecholamine (both adrenaline and noradrenaline) and cortisol concentrations in women undergoing hysterectomy. Nevertheless, the magnitude of difference in adrenaline between the groups in our review was around 8%, which may be regarded as clinically small. Another potential mechanism may relate to calcium channel inhibition. As calcium channel blockers can attenuate the hemodynamic response and share a target mechanism with gabapentin, this may produce similar effects in a clinical population.

Our meta-regression analysis found that a gabapentin dose was associated with greater attenuation of HR, with higher doses producing lower HRs when compared with control. A previous meta-regression has shown a similar effect when evaluating lower morphine consumption during the postoperative period. These meta-regression results suggest that future studies should aim to use higher doses in order to improve the absolute effects of gabapentin on HR responses. Nevertheless, the oral route of gabapentin used in the included studies has implications for its use in high-risk patients, which may be prohibitive in emergency surgery. In addition, it is unclear whether titration of the gabapentin dosage would alter efficacy, an issue raised in the first POISE study. Moreover, it is unclear whether such increases in dose would affect the incidence of bradycardia and hypotension, which may have been responsible for the increased mortality in POISE. With regard to the pharmacokinetics of gabapentin, bioavailability is known to decrease with increasing dosages, therefore plasma concentrations may not reflect
Gabapentin for intubation

the dose administered. Baseline hemodynamic variables recorded before induction were not associated with greater attenuation of hemodynamic variables on meta-regression analysis. This suggests that similar differences would be achieved regardless of the baseline blood pressure or HR of the participants. Despite this, it should be emphasized that most of the included studies comprised low-risk non-hypertensive patients, and therefore, the range of baseline values was limited. Furthermore, our meta-regression analysis may be underpowered to detect associations for these outcomes.

Gabapentin was found to reduce the risk of hypertension or tachycardia requiring treatment. This result is intuitive given the observed effects of gabapentin on HR and blood pressure. Nevertheless, data from the studies included in this review are limited with regard to episodes of bradycardia or hypotension. Indeed, one study in the review excluded three patients from the analysis due to hypotension, and one study excluded a patient due to an episode of bradycardia. The former study was not included in the meta-analysis as it did not report whether these patients required treatment. As intraoperative hypotension may be associated with stroke, myocardial injury, acute kidney injury, and mortality, future studies with gabapentin should aim to report these outcomes. These studies should be well designed (with full intention-to-treat analysis) and adequately powered to detect differences in these clinically important outcomes and avoid reporting surrogate outcomes such as hemodynamic measurements. For example, we calculated a required information size of 558 participants to provide a definitive answer for our outcome of hypertension or tachycardia (requiring treatment).

As previously stated, future research should aim to report the incidences of adverse events associated with the use of gabapentin in the perioperative period, particularly as these may be associated with perioperative mortality. This would have implications for the use of gabapentin for attenuating the hemodynamic response to intubation as well as for using it more widely in postoperative pain control. Clinical trials should aim to address issues with internal validity, such as the use of identical placebo controls, intention-to-treat analysis of participants suffering adverse events, and adequate allocation concealment. Ultimately, adequately powered randomized-controlled trials should examine the effects of gabapentin in high-risk patients (such as those with previous myocardial infarction or ischemic heart disease) and determine effects on clinically relevant outcomes, such as mortality, myocardial infarction, arrhythmia and myocardial ischemia, while avoiding reporting surrogate variables as primary outcomes.

In conclusion, it remains unknown whether gabapentin improves clinically relevant outcomes such as death and myocardial infarction since studies failed to report on these. Nevertheless, this review has found evidence that gabapentin reduces HR and blood pressure responses to intubation. Even so, caution is advised with these results as there are few data from trials with a low risk of bias that focus on adverse hemodynamic events in high-risk patients. This novel meta-analysis shows the beneficial effects of gabapentin in attenuating the hemodynamic response to intubation.

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Editorial responsibility This submission was handled by Dr. Philip M. Jones, Associate Editor, Canadian Journal of Anesthesia.

Appendix: MEDLINE search

1. gabapentin.ti,ab
2. neurontin.ti,ab
3. 1 OR 2
4. intubation.ti,ab
5. exp INTUBATION, INTRATRACHEAL/
6. 4 OR 5
7. 3 AND 6

References


Gabapentin for intubation


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