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REVIEW ARTICLE/BRIEF REVIEW

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Source *We searched MEDLINE®, EMBASE™, CINAHL, AMED, and unpublished clinical trial databases for randomized-controlled trials that compared gabapentin with control, fentanyl, clonidine, or beta blockers for attenuating the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'étalon 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 bêta-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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principaux critères d'évaluation. Les critères d'évaluation secondaires étaient les changements hémodynamiques suite à l'intubation.

Constatations principales *Nous avons inclus 29 études randomisées, dont deux seulement affichaient un risque faible de biais. Aucune donnée n'était fournie concernant les critères d'évaluation principaux et aucune étude n'incluait de patients à risque élevé. L'utilisation de la gabapentine a entraîné une atténuation de l'augmentation de la tension artérielle moyenne [différence moyenne (DM), −12 mmHg; intervalle de confiance (IC) 95 %, −17 à −8] et de la fréquence cardiaque (DM, −8 battements·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, étant 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

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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,[12] 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.[13] We used the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) Working Group criteria to assess the quality of evidence for each outcome.[14] 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 I^2 statistic with a corresponding *P* value derived from the Chi square statistic. We regarded I^2 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

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study effects, including possible publication bias, using Egger's linear regression test.[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.[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.[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,[18] Comprehensive Meta-Analysis V3.3,[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).[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

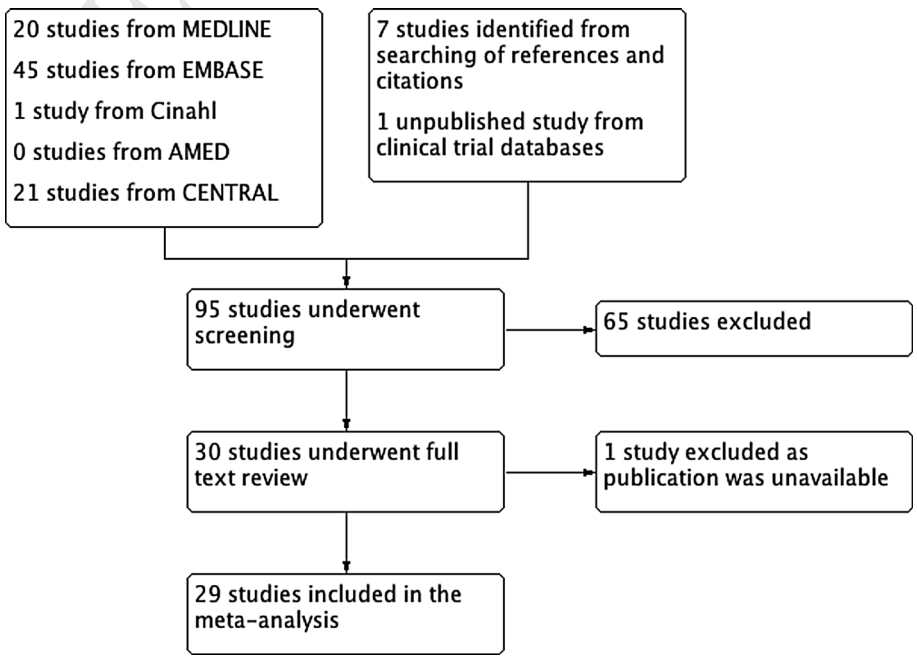

Fig. 1 PRISMA flowchart for included studies

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Table Baseline characteristics of included studies

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, Baduni 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 $mg \cdot kg^{-1}$) 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 $mg \cdot kg^{-1}$) and glycopyrrolate (0.004 $mg \cdot kg^{-1}$)
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 $mg \cdot kg^{-1}$)
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 $mg \cdot kg^{-1}$)
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 Saliminia 2009	32.8	51%	75	900 mg gabapentin 2 hr before surgery	1) Placebo 2) 200 μg clonidine	Iran	Midazolam (0.03 $mg \cdot kg^{-1}$)
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

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Study name	Mean age	Female (%)	*n*	Intervention	Comparator	Country	Perioperative medication
Parida *et al.* 2015	37.9	58%	50	800 mg gabapentin 2 hr before surgery	1) Placebo 2) fentanyl	India	Diazepam (0.2 $mg \cdot kg^{-1}$), omeprazole (20 mg) and metoclopramide (10 mg)
Sanabria Siacara and Pena 2013	31.5	37%	30	600 mg gabapentin 1 hr before surgery	Clonidine 2 $\mu g \cdot kg^{-1}$	Mexico	Midazolam (0.02 $mg \cdot kg^{-1}$)
Sharma *et al.* 2012	37.6	NR	120	800 mg gabapentin 1 hr before induction	1) Placebo 2) 300 μg clonidine 3) 400 mg gabapentin and 150 μg clonidine	Kashmir	Metoclopramide (10 mg)
Shreedhara *et al.* 2014	40.4	48%	90	900 mg gabapentin 2 hr before surgery	1) Placebo 2) 200 μg clonidine	India	Glycopyrrolate (4 $\mu g \cdot kg^{-1}$), ranitidine (1 $mg \cdot kg^{-1}$) and ondansetron (0.08 $mg \cdot kg^{-1}$)
Shrestha, Marhatta and Amatya 2009	33.8	NR	72	1,200 mg gabapentin 2 hr before induction	1) Placebo 2) esmolol	Nepal	None
Singhal, Kaur and Arora 2014	32.8	63%	100	900 mg gabapentin 90 min before surgery	Clonidine 200 μg	India	None
Soltanzadeh *et al.* 2012	28.4	50%	90	900 mg gabapentin 2 hr before surgery	Placebo	Iran	Midazolam (0.05 $mg \cdot kg^{-1}$)
Zia *et al.* 2012	36.7	40%	110	800 mg gabapentin 2 hr before surgery	Placebo	Pakistan	None

Study name	Anesthetic and muscle relaxant	Maintenance	Laryngoscope and tube	Participant population	Type of surgery	Duration of intubation
Abdel-Halim *et al.* 2009	Fentanyl (1.5-2 $\mu g \cdot kg^{-1}$), thiopentone (3-7 $mg \cdot kg^{-1}$) and atracurium (5 $mg \cdot kg^{-1}$)	Isoflurane	NR	ASA I and II, aged 18-65 yr, excluded patients with hypertension and cardiac disease	Mastectomy	NR
Aggarwal, Baduni and Jain 2015	Thiopentone and rocuronium	Nitrous oxide	Macintosh 3 and 7 mm or 8 mm endotracheal tube	ASA I and II, aged 18-45 yr	Laparoscopic cholecystectomy	NR
Ali *et al.* 2009	Propofol (2 $mg \cdot kg^{-1}$) and vecuronium (0.08 $mg \cdot kg^{-1}$)	Sevoflurane and nitrous oxide	Macintosh 3 and 7 mm or 8 mm endotracheal tube	ASA I, aged 20-40 yr, normotensive, excluded those with cardiovascular disease	Elective surgery (hernioplasty, arthroscopy, cholecystectomy and vitrectomy)	Patients excluded if longer than 15 sec
Ali, Elnakera and Samir 2013	Fentanyl (2 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and cisatracurium (0.15 $mg \cdot kg^{-1}$)	Isoflurane	NR	ASA I and II, 18-60 yr, excluded patients with hypertension	Elective cataract surgery	Patients excluded if more than one attempt

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Study name	Anesthetic and muscle relaxant	Maintenance	Laryngoscope and tube	Participant population	Type of surgery	Duration of intubation
Ayatollahi *et al.* 2014	Fentanyl (1.5 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Isoflurane and nitrous oxide	Fixed laryngoscope and 5-5.5 mm endotracheal tube	ASA I and II, aged 30-70 yr	Microlaryngeal surgery	NR
Bafna, Goyal and Garg 2011	Fentanyl (1 $\mu g \cdot kg^{-1}$), thiopentone (5 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Isoflurane, nitrous oxide and atracurium	Appropriately sized endotracheal tube	ASA I and II, aged 20-60 yr, normotensive, excluded those with cardiovascular disease and hypertension	Elective surgery	Patients excluded if longer than 30 sec or more than one attempt
Bala, Bharti and Ramesh 2015	Thiopentone (5 $mg \cdot kg^{-1}$), fentanyl (2 $\mu g \cdot kg^{-1}$) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Isoflurane and nitrous oxide	NR	Hypertensive patients, aged 35-60 yr	Elective surgery	Patients excluded if longer than 30 sec or more than one attempt
Bhandari and Shahi 2013	Tramadol (2 $mg \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Halothane and nitrous oxide	NR	ASA I, aged 16-60 yr, excluded patients on anti-hypertensives	Elective surgery	Patients excluded if longer than 30 sec or more than one attempt
Bhandari *et al.* 2014	Fentanyl (3 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and vecuronium (800 $\mu g \cdot kg^{-1}$)	Isoflurane and nitrous oxide	NR	ASA I and II, aged 18-60 yr, excluded patients on anti-hypertensives	Laparoscopic cholecystectomy	Patients excluded if more than one attempt
Bharti *et al.* 2013	Fentanyl (2 $\mu g \cdot kg^{-1}$), propofol (20 mg boluses to BIS target of 60) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Propofol and nitrous oxide	NR	ASA I and II, aged 30-60 yr	Mastectomy for breast cancer	NR
Farzi *et al.* 2015	Propofol (2-2.5 $mg \cdot kg^{-1}$), fentanyl (2 $\mu g \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Propofol and remifentanil TIVA	NR	ASA I and II, aged 18-45 yr	Septorhinoplasty	NR
Fassoulaki *et al.* 2006	Propofol (2.5 $mg \cdot kg^{-1}$) and cisatracurium (0.15 $mg \cdot kg^{-1}$)	NR	NR	ASA I and II, aged <60 yr	Abdominal hysterectomy	NR

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Study name	Anesthetic and muscle relaxant	Maintenance	Laryngoscope and tube	Participant population	Type of surgery	Duration of intubation
Iftikhar *et al.* 2011	Nalbuphine (0.1 $mg \cdot kg^{-1}$), thiopentone (5 $mg \cdot kg^{-1}$) and rocuronium (0.6 $mg \cdot kg^{-1}$)	NR	NR	ASA I and II, excluded patients with hypertension, ischemic heart disease and extremes of age	Elective surgery	NR
Kaya *et al.* 2008	Fentanyl (2 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Sevoflurane and 50% nitrous oxide	Macintosh 3 and 7 mm or 8 mm endotracheal tube	Normotensive, ASA I and II	Elective surgery	NR
Kiran and Verma 2008	Propofol (2.5 $mg \cdot kg^{-1}$) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Halothane and nitrous oxide	NR	ASA I and II, aged 20-50 yr, excluded patients with hypertension	Elective surgery	NR
Koç, Memis and Sut 2007	Remifentanil (0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Propofol, remifentanil and nitrous oxide	Macintosh 3 and 8 mm endotracheal tube	ASA I, normotensive, excluded those with cardiac disease	Varicocele surgery	NR
Kumari and Pathania 2009	Tramadol (100 mg), propofol (2 $mg \cdot kg^{-1}$) and rocuronium (0.9 $mg \cdot kg^{-1}$)	Propofol and nitrous oxide	NR	ASA I and II, excluded patients with cardiac disease	Elective surgery	Patients excluded if longer than 30 sec or more than one attempt
Marashi, Ghafari and Saliminia 2009	Fentanyl (2.5 $\mu g \cdot kg^{-1}$), thiopental sodium (0.5 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	NR	Macintosh 3 and 7.5-8 mm endotracheal tube	ASA I and II, aged <45 yr, excluded patients with hypertension and cardiovascular disease	Elective orthopedic and general surgery	Patients excluded if longer than 30 sec
Memiş *et al.* 2006	Propofol (2 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Sevoflurane and nitrous oxide	Macintosh 3 and 7 mm or 8 mm endotracheal tube	ASA I, normotensive, excluded patients with cardiac disease	Elective surgery	NR
Montazeri *et al.* 2011	Fentanyl (3 $\mu g \cdot kg^{-1}$), thiopental (5 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	Propofol and nitrous oxide	Macintosh 3	ASA I and II, aged 18-65 yr, excluded patients with hypertension or cardiovascular disease	Elective surgery	Patients excluded if longer than 15 sec

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Table continued

Study name	Anesthetic and muscle relaxant	Maintenance	Laryngoscope and tube	Participant population	Type of surgery	Duration of intubation
Neogi *et al.* 2012	Fentanyl (2 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$ and rocuronium (0.7 $mg \cdot kg^{-1}$)	Isoflurane and nitrous oxide	NR	ASA I and II, aged 18-65 yr, excluded patients with hypertension and cardiac dysfunction	Laparoscopic cholecystectomy	NR
Parida *et al.* 2015	Fentanyl (2 $\mu g \cdot kg^{-1}$), thiopentone (5 $mg \cdot kg^{-1}$), vecuronium (0.1 $mg \cdot kg^{-1}$)	Isoflurane and nitrous oxide	Macintosh	ASA I, aged 20-50 yr, elective non-cardiac surgery	Elective non-cardiac surgery	Patients excluded if longer than 30 sec
Sanabria Siacara and Pena 2013	Fentanyl (3 $\mu g \cdot kg^{-1}$), propofol (2 $mg \cdot kg^{-1}$) and vecuronium (100 $\mu g \cdot kg^{-1}$)	Sevoflurane and fentanyl	NR	ASA I and II, aged 18-50 yr, excluded patients with hypertension, cardiac disease or on anti-hypertensives	Elective surgery	NR
Sharma *et al.* 2012	Propofol (2.5 $mg \cdot kg^{-1}$) and rocuronium (0.9 $mg \cdot kg^{-1}$)	Isoflurane/halothane and nitrous oxide	NR	ASA I and II, aged 20-60 yr, excluded patients on anti-hypertensives	Elective surgery	Patients excluded if longer than 30 sec
Shreedhara *et al.* 2014	Propofol (2 $mg \cdot kg^{-1}$) and suxamethonium (2 $mg \cdot kg^{-1}$)	Isoflurane and nitrous oxide	NR	ASA I and II, aged 18-60 yr	Elective surgery	NR
Shrestha, Marhatta and Amatya 2009	Pethidine (0.75 $mg \cdot kg^{-1}$), propofol (2-2.5 $mg \cdot kg^{-1}$) and vecuronium (0.1 $mg \cdot kg^{-1}$)	Halothane	NR	ASA I and II, aged <65 yr, patients with cardiopulmonary disease excluded	Elective surgery	Patients excluded if longer than 30 sec or more than one attempt
Singhal, Kaur and Arora 2014	Thiopentone (5 $mg \cdot kg^{-1}$) and succinylcholine (2 $mg \cdot kg^{-1}$)	Halothane and nitrous oxide	7-8 mm endotracheal tube	ASA I and II, aged 20-50 yr, excluded patients with hypertension	Elective surgery	NR
Soltanzadeh *et al.* 2012	Fentanyl (2 $\mu g \cdot kg^{-1}$), thiopental (5 $mg \cdot kg^{-1}$) and atracurium (0.5 $mg \cdot kg^{-1}$)	NR	Macintosh 3 and 7.5-8 mm endotracheal tube	ASA I and II, aged 15-50 yr, excluded patients with hypertension and ischemic heart disease	Elective surgery	Patients excluded if more than one attempt

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Table continued

Study name	Anesthetic and muscle relaxant	Maintenance	Laryngoscope and tube	Participant population	Type of surgery	Duration of intubation
Zia *et al.* 2012	NR	NR	NR	ASA I and II, aged 20-40 yr, excluded patients with hypertension and cardiovascular disease	Elective surgery (2-3 hr)	NR

ASA = American Society of Anesthesiologists; BIS = bispectral index; NR = not reported; TIVA = total intravenous anesthesia; TID = three times a day

studies involving patients at high risk for adverse cardiac outcomes. One study included patients with hypertensive disease,[26] and one study used invasive blood pressure monitoring to record hemodynamic variables.[22] Only one study provided details of the equipment used to measure noninvasive blood pressure.[33] 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.[35,41] 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[21,22,25,26,33,35,38,39,41] 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[21-24,26,28-30,32-39,41,43-45,47] 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[21-23,26,28,30,32-39,41,43,44,47] 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

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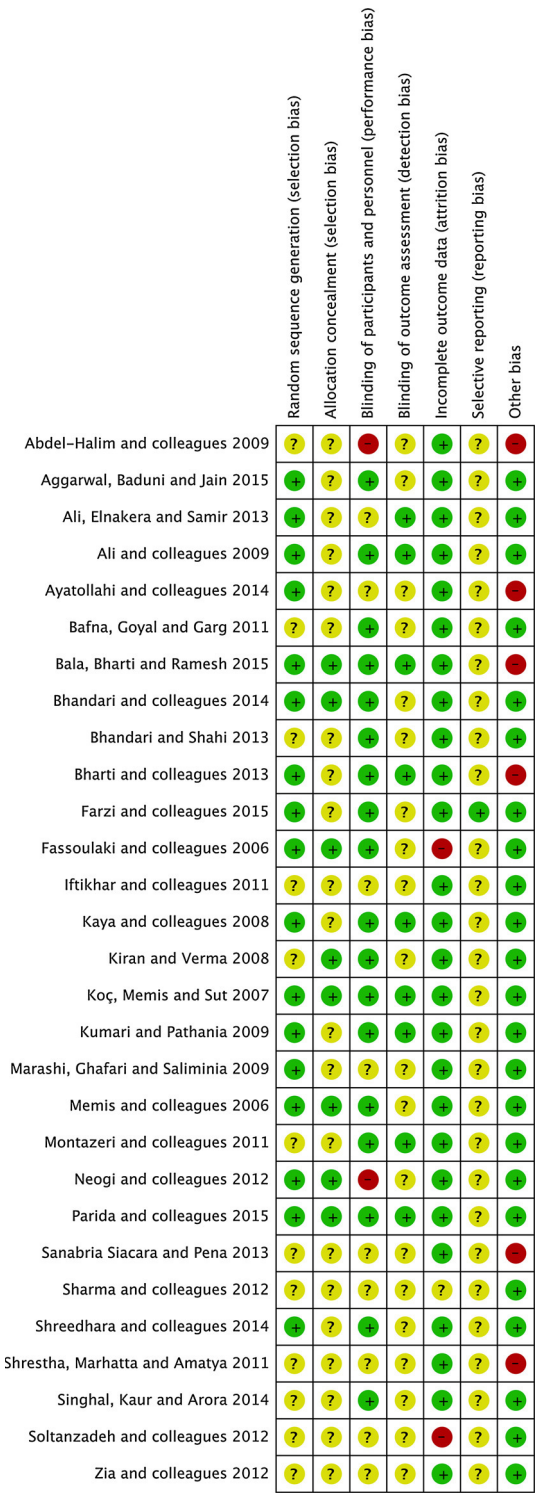

Fig. 2 Risk of bias for included studies. Green indicates low risk, yellow indicates unclear risk, and red indicates high risk

that gabapentin crossed the O'Brien-Fleming monitoring boundary for benefit for each time point. In addition, the required information size was reached for one, five, and ten minutes (909, 824, and 432 participants, respectively).

Heart rate 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[20-39,41,43-45,47] 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[20-23,25-28,30-39,41,43,44,47] 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 (I^2 = 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 (R^2 = 35%; $P = 0.006$), five minutes (R^2 = 38%; $P = 0.02$), and ten minutes (R^2 = 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[20,21,24,27,28,31,32,34,36,37,43-45,47,48] 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[20,21,24,27,28,30-32,34,36,37,43-45,47] 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[20,21,27,28,30-32,34,36,37,43,44,47] 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 (I^2 = 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

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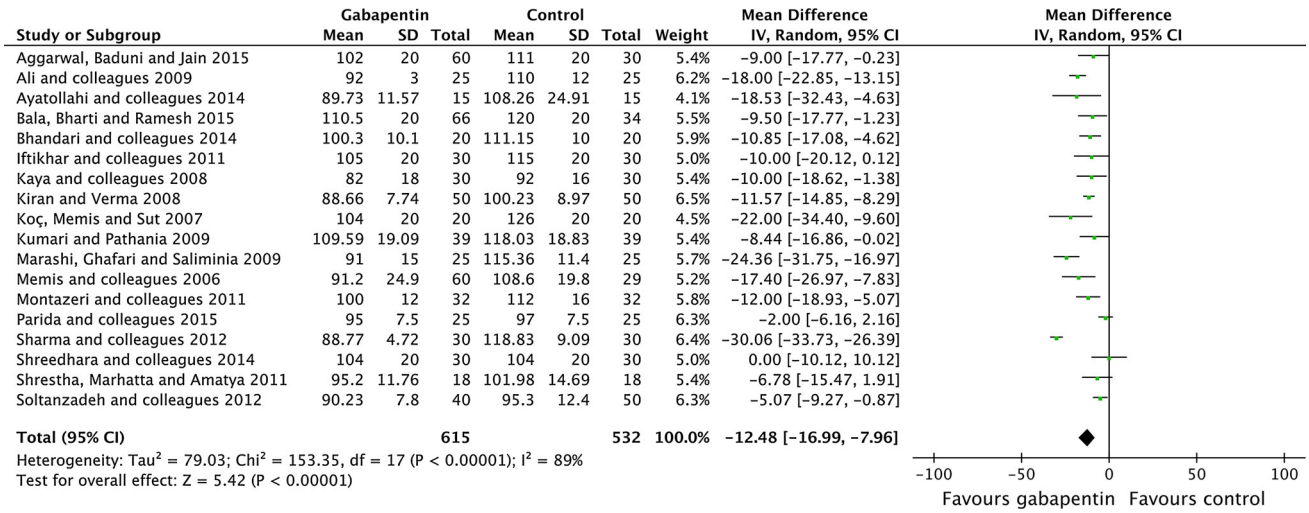

Fig. 3 Forest plot of gabapentin effects on mean arterial pressure at one minute

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[20,21,24,27,28,31,32,34,36,37,43,44,47,48] 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[20,21,24,27,28,30-32,34,36,37,43,44,47] 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[20,21,27,28,30-32,34,36,37,43,44,47] 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

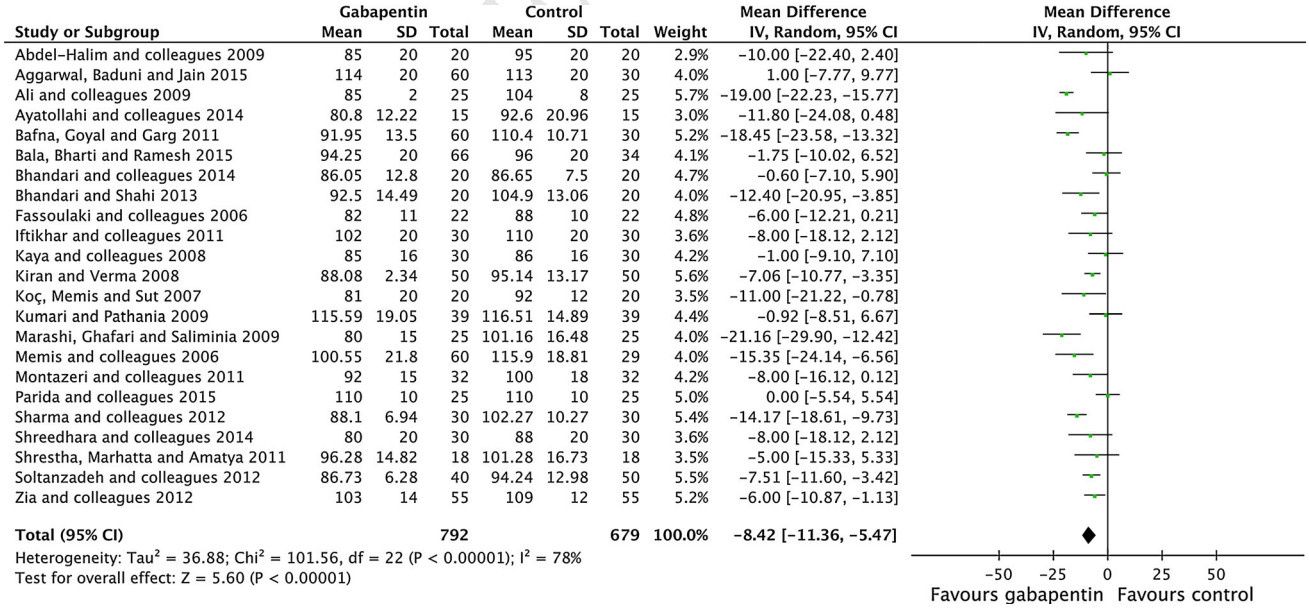

Fig. 4 Forest plot of gabapentin effects on heart rate at one minute

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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[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[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[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;[22,38] HR > 130 beats·min^{-1}, SBP > 200 mmHg or > 30% increase from baseline for more than 60 sec;[26] MAP or HR >20% of baseline;[29] MAP > 110 mmHg.[40]

One study[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[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[37,39,42-44] (MD, 5 beats·min^{-1}; 95% CI, 3 to 7; moderate quality). One study[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.[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,[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.[49] Indeed, only two studies[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.[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

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intravenous fentanyl, 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.[50] In high-risk patients, such increases can lead to myocardial ischemia and therefore myocardial infarction.[1,51,52] Many agents have been used to attenuate the hemodynamic response to intubation and thus aim to reduce myocardial ischemia.[2] Although agents such as clonidine[53] 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[4] and increases in clinically important hypotension and non-fatal cardiac arrest with clonidine.[6] 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,[3] 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,[8] attenuate the hemodynamic response to intubation, and reduce catecholamine and cortisol responses postoperatively;[54] 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.[8] 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.[8,55] 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[8,56-58] (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.[22] Previous *in vitro* research has suggested that gabapentin may inhibit the release of catecholamines from adrenal chromaffin cells,[59] 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.[54] 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.[60]

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.[8] 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.[4] 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

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the dose administered.[61] 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,[47] and one study excluded a patient due to an episode of bradycardia.[31] 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,[62] myocardial injury, acute kidney injury,[63] and mortality,[64] 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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Conflicts of interest None declared.

Author contributions *Brett Doleman* developed the concept for this review and wrote the manuscript. *Matthew Sherwin, Jonathan N. Lund,* and *John P. Williams* participated in editing the manuscript. All authors contributed to the data analysis.

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

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