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1 REVIEW ARTICLE/BRIEF REVIEW

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

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

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8

11 **Abstract**
12 **Purpose** *Endotracheal intubation is the gold standard for*
13 *securing the airway before surgery. Nevertheless, this*
14 *procedure can produce an activation of the sympathetic*
15 *nervous system and result in a hemodynamic response*
16 *which, in high-risk patients, may lead to cardiovascular*
17 *instability and myocardial ischemia. The aim of this review*
18 *was to evaluate whether gabapentin can attenuate this*
19 *response and whether such an attenuation could translate*
20 *into reduced myocardial ischemia and mortality.*
21 **Source** *We searched MEDLINE®, EMBASE^TM, CINAHL,*
22 *AMED, and unpublished clinical trial databases for*
23 *randomized-controlled trials that compared gabapentin*
24 *with control, fentanyl, clonidine, or beta blockers for*
25 *attenuating the hemodynamic response to intubation.*
26 *Primary outcomes were mortality, myocardial infarction,*
27 *and myocardial ischemia. Secondary outcomes were*
28 *hemodynamic changes following intubation.*
29 **Principal findings** *We included 29 randomized trials with*
30 *only two studies at low risk of bias. No data were provided*
31 *for the primary outcomes and no studies included high-risk*
32 *patients. The use of gabapentin resulted in attenuation in*
33 *the rise in mean arterial blood pressure [mean difference*
34 *(MD), −12 mmHg; 95% confidence interval (CI), −17 to*
35 *−8] and heart rate (MD, −8 beats·min^{−1}; 95% CI, −11 to*
36 *−5) one minute after intubation. Gabapentin also reduced*
37 *the risk of hypertension or tachycardia requiring treatment*
38 *(risk ratio, 0.15; 95% CI, 0.05 to 0.48). Data were limited*
39 *on adverse hemodynamic events such as bradycardia and*
40 *hypotension.*
41 **Conclusion** *It remains unknown whether gabapentin*
42 *improves clinically relevant outcomes such as death and*
43 *myocardial infarction since studies failed to report on*
44 *these. Nevertheless, gabapentin attenuated increases in*
45 *heart rate and blood pressure following intubation when*
46 *compared with the control group. Even so, the studies*
47 *included in this review were at potential risk of bias.*
48 *Moreover, they did not include high-risk patients or report*
49 *adverse hemodynamic outcomes. Future studies are*
50 *required to address these limitations.*
51

52 **Résumé**
53 **Objectif** *L'intubation endotrachéale constitue l'étalon or*
54 *de la prise en charge des voies aériennes avant une*
55 *chirurgie. Toutefois, cette intervention peut entraîner une*
56 *activation du système nerveux sympathique et provoquer*
57 *une réponse hémodynamique qui, chez les patients courant*
58 *un risque élevé, pourrait mener à une instabilité*
59 *cardiovasculaire et une ischémie myocardique. L'objectif*
60 *de ce compte rendu était d'examiner si la gabapentine*
61 *pouvait atténuer cette réponse et si une telle atténuation*
62 *pouvait se traduire en une réduction de l'ischémie*
63 *myocardique et de la mortalité.*
64 **Source** *Nous avons effectué des recherches dans les bases*
65 *de données MEDLINE®, EMBASE^TM, CINAHL, AMED,*
66 *ainsi que dans les bases de données d'études cliniques non*
67 *publiées afin d'en extraire les études randomisées*
68 *contrôlées comparant la capacité de la gabapentine par*
69 *rapport à un groupe témoin, au fentanyl, à la clonidine ou*
70 *à des bêta-bloquants, à atténuer la réponse*
71 *hémodynamique à l'intubation. La mortalité, l'infarctus*
72 *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

172 intravenous fentanyl as a comparison due to its use as the
173 standard agent at induction of anesthesia. We searched the
174 following databases: MEDLINE® (1946-September 2015)
175 (Appendix), EMBASE™ (1974- September 2015),
176 CINAHL (1981- September 2015), AMED (1985-
177 September 2015), and CENTRAL (until September
178 2015). We searched for studies using the keywords in the
179 title and abstract, *gabapentin, Neurontin, and intubation*.
180 The MeSH terms *intubation* and *intratracheal* were
181 exploded and combined with the above terms. We also
182 searched for unpublished studies from Clinicaltrials.gov,
183 the ISRCTN registry, and the WHO international clinical
184 trials registry. Furthermore, we searched the reference lists
185 of the identified studies and used Google Scholar to
186 identify studies that had cited those included. We contacted
187 the authors if further information was required.

188 ### Inclusion criteria

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

202 ### Outcomes

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

220 ### Data extraction and risk of bias

221 Two study authors (B.D. and M.S.) extracted the following
222 information onto an electronic database: study name, year
223 of publication, mean age of participants, percentage of
224 female participants, sample size, intervention, comparator,
225 country, perioperative medication, induction agents,
226 maintenance agents, laryngoscope and endotracheal tube
227 used, participant population, type of surgery, and duration
228 of intubation. The same two authors assessed risk of bias
229 using the Cochrane tool for assessing risk of bias,[12] and
230 agreement was reached by consensus. We assessed the
231 following domains: randomization, allocation
232 concealment, blinding, attrition bias, selective outcome
233 reporting, and other sources of bias. These domains were
234 assessed as low risk, unclear risk, and high risk and
235 presented in a risk of bias table.

236 ### Statistical analysis

237 We present continuous outcomes using mean difference
238 (MD) and dichotomous outcomes using risk ratios (RR).
239 The precision of outcomes is presented with 95%
240 confidence intervals (95% CI). We regarded a 10%
241 relative risk difference in dichotomous outcomes, a 10
242 mmHg MD in blood pressure, and 5 beats·min^{-1} MD in
243 HR as clinically significant. We were unaware of any data
244 directly linking changes in hemodynamic variables and risk
245 of myocardial events, and therefore, these values for
246 clinical significance were not empirically derived. Where
247 data were not presented, authors were contacted to provide
248 further information. If no response was received, the results
249 were extracted from published graphs. If standard
250 deviations were not published, we estimated these from
251 other studies in the meta-analysis.[13] We used the Grading
252 of Recommendations, Assessment, Development and
253 Evaluations (GRADE) Working Group criteria to assess
254 the quality of evidence for each outcome.[14] The evidence is
255 downgraded owing to any concerns regarding the
256 indirectness of evidence, lack of precision in effect
257 estimates, potential publication bias, unexplained
258 heterogeneity, and risk of bias in results. This is a
259 qualitative downgrading from high quality to moderate,
260 low, or very low quality dependent on the concerns cited
261 above. We made no statistical adjustment of results.

262 Data were aggregated using a random effects model due
263 to substantial clinical heterogeneity in the gabapentin dose
264 and baseline hemodynamic variables of the participants.
265 Statistical heterogeneity is presented using the I^2 statistic
266 with a corresponding P value derived from the Chi square
267 statistic. We regarded I^2 of > 50% or $P < 0.10$ as evidence
268 of statistical heterogeneity. When more than ten studies
269 were included in the meta-analysis, we assessed small

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

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

7 studies identified from searching of references and citations

1 unpublished study from clinical trial databases

95 studies underwent screening

65 studies excluded

30 studies underwent full text review

1 study excluded as publication was unavailable

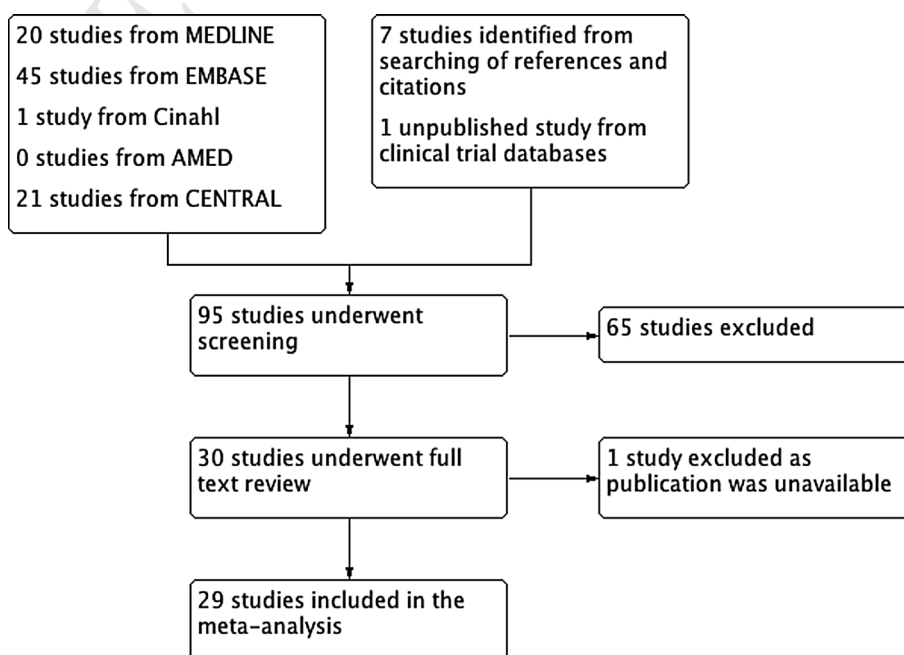29 studies included in the meta−analysis

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·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 Saliminia 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

Table continued

Study name	Mean age	Female (%)	n	Anesthetic and muscle relaxant	Intervention	Maintenance	Laryngoscope and tube	Participant population	Comparator	Type of surgery	Country	Perioperative medication	Duration of intubation
Parida et al. 2015	37.9	58%	50		800 mg gabapentin 2 hr before surgery				1) Placebo 2) fentanyl		India	Diazepam (0.2 mg·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 µg·kg⁻¹		Mexico	Midazolam (0.02 mg·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 µg·kg⁻¹), ranitidine (1 mg·kg⁻¹) and ondansetron (0.08 mg·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·kg⁻¹)	
Zia et al. 2012	36.7	40%	110		800 mg gabapentin 2 hr before surgery				Placebo		Pakistan	None	
Abdel-Halim et al. 2009				Fentanyl (1.5-2 µg·kg⁻¹), thiopentone (3-7 mg·kg⁻¹) and atracurium (5 mg·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			
Ali et al. 2009				Propofol (2 mg·kg⁻¹) and vecuronium (0.08 mg·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 µg·kg⁻¹), propofol (2 mg·kg⁻¹) and cisatracurium (0.15 mg·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

Table continued

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 µg·kg^{-1}), propofol (2 mg·kg^{-1}) and atracurium (0.5 mg·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 µg·kg^{-1}), thiopentone (5 mg·kg^{-1}) and atracurium (0.5 mg·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·kg^{-1}), fentanyl (2 µg·kg^{-1}) and vecuronium (0.1 mg·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·kg^{-1}), propofol (2 mg·kg^{-1}) and vecuronium (0.1 mg·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 µg·kg^{-1}), propofol (2 mg·kg^{-1}) and vecuronium (800 µg·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 µg·kg^{-1}), propofol (20 mg boluses to BIS target of 60) and vecuronium (0.1 mg·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·kg^{-1}), fentanyl (2 µg·kg^{-1}) and atracurium (0.5 mg·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·kg^{-1}) and cisatracurium (0.15 mg·kg^{-1})	NR	NR	ASA I and II, aged <60 yr	Abdominal hysterectomy	NR

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Table continued

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·kg⁻¹), thiopentone (5 mg·kg⁻¹) and rocuronium (0.6 mg·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 µg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (0.1 mg·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·kg⁻¹) and vecuronium (0.1 mg·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 µg·kg⁻¹·min⁻¹), propofol (2 mg·kg⁻¹) and atracurium (0.5 mg·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·kg⁻¹) and rocuronium (0.9 mg·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 µg·kg⁻¹), thiopental sodium (0.5 mg·kg⁻¹) and atracurium (0.5 mg·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·kg⁻¹) and atracurium (0.5 mg·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 µg·kg⁻¹), thiopental (5 mg·kg⁻¹) and atracurium (0.5 mg·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 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and rocuronium (0.7 mg·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 μg·kg⁻¹), thiopentone (5 mg·kg⁻¹), vecuronium (0.1 mg·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 μg·kg⁻¹), propofol (2 mg·kg⁻¹) and vecuronium (100 μg·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·kg⁻¹) and rocuronium (0.9 mg·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·kg⁻¹) and suxamethonium (2 mg·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·kg⁻¹), propofol (2-2.5 mg·kg⁻¹) and vecuronium (0.1 mg·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·kg⁻¹) and succinylcholine (2 mg·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 μg·kg⁻¹), thiopental (5 mg·kg⁻¹) and atracurium (0.5 mg·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

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

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

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

Heart rate Gabapentin attenuated the rise in HR at one 382
minute after intubation when compared with the control 383
group (MD, -8 beats·min^{-1}; 95% CI, -11 to -5; 384
moderate quality). At five minutes, the analysis included 385
25 studies[20-39,41,43-45,47] with 1,564 participants where the 386
aggregated effect estimate showed an attenuated rise with 387
gabapentin (MD, -6 beats·min^{-1}; 95% CI, -8 to -4; 388
moderate quality). At ten minutes, the analysis included 22 389
studies[20-23,25-28,30-39,41,43,44,47] with 1,458 participants 390
where the aggregated effect estimate showed an 391
attenuated rise with gabapentin (MD, -5 beats·min^{-1}; 392
95% CI, -7 to -3; moderate quality) (Fig. 4). **AQ1** 393

There was evidence of statistical heterogeneity at all 394
time points ($I^2 = 46\text{-}76\%$; $P < 0.01$). There was evidence of 395
small study effects at one and five minutes ($P = 0.05$ and P 396
$= 0.004$, respectively); however, the missing studies were 397
to the left of the mean, suggesting a bias against 398
gabapentin. On meta-regression analysis, an increase in 399
the gabapentin dose predicted greater attenuation in HR at 400
one minute ($R^2 = 35\%$; $P = 0.006$), five minutes ($R^2 = 38\%$; 401
$P = 0.02$), and ten minutes ($R^2 = 52\%$; $P = 0.004$). Baseline 402
HR was not a significant predictor at any time point. Trial 403
sequential analysis showed that gabapentin crossed the 404
O'Brien-Fleming boundary for benefit at all time points. In 405
addition, the results for five and ten minutes reached the 406
required information size (1,339 and 784 participants, 407
respectively). Nevertheless, the results for one minute 408
failed to reach the required information size (2,022 409
participants). 410

Systolic blood pressure At one minute after intubation, 411
the analysis included 15 412
studies[20,21,24,27,28,31,32,34,36,37,43-45,47,48] with 928 413
participants where the aggregated effect estimate showed 414
gabapentin attenuated the rise in SBP when compared with 415
the control group (MD, -16 mmHg; 95% CI, -22 to -9; 416
low quality). At five minutes, the analysis included 15 417
studies[20,21,24,27,28,30-32,34,36,37,43-45,47] with 921 participants 418
where the aggregated effect estimate showed an attenuated 419
rise with gabapentin (MD, -10 mmHg; 95% CI, -16 to 420
-4; low quality). At ten minutes, the analysis included 13 421
studies[20,21,27,28,30-32,34,36,37,43,44,47] with 855 participants 422
where the aggregated effect estimate showed an attenuated 423
rise with gabapentin (MD, -9 mmHg; 95% CI, -16 to -2; 424
low quality). 425

There was evidence of substantial statistical 426
heterogeneity at all time points ($I^2 = 89\text{-}94\%$; $P <$ 427
0.001). There was no evidence of small study effects at 428
one ($P = 0.27$), five ($P = 0.43$), or ten minutes ($P = 0.30$). 429
On meta-regression analysis, gabapentin dose and baseline 430
SBP did not significantly predict gabapentin effect. Trial 431
sequential analysis showed that gabapentin crossed the 432
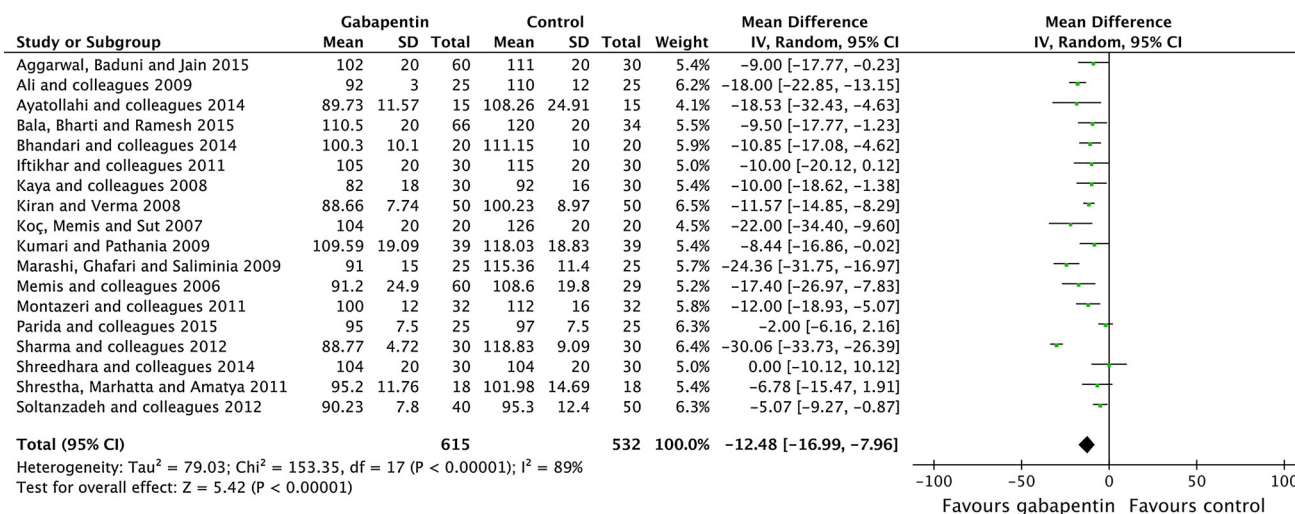O'Brien-Fleming boundary for benefit at one and five 433

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
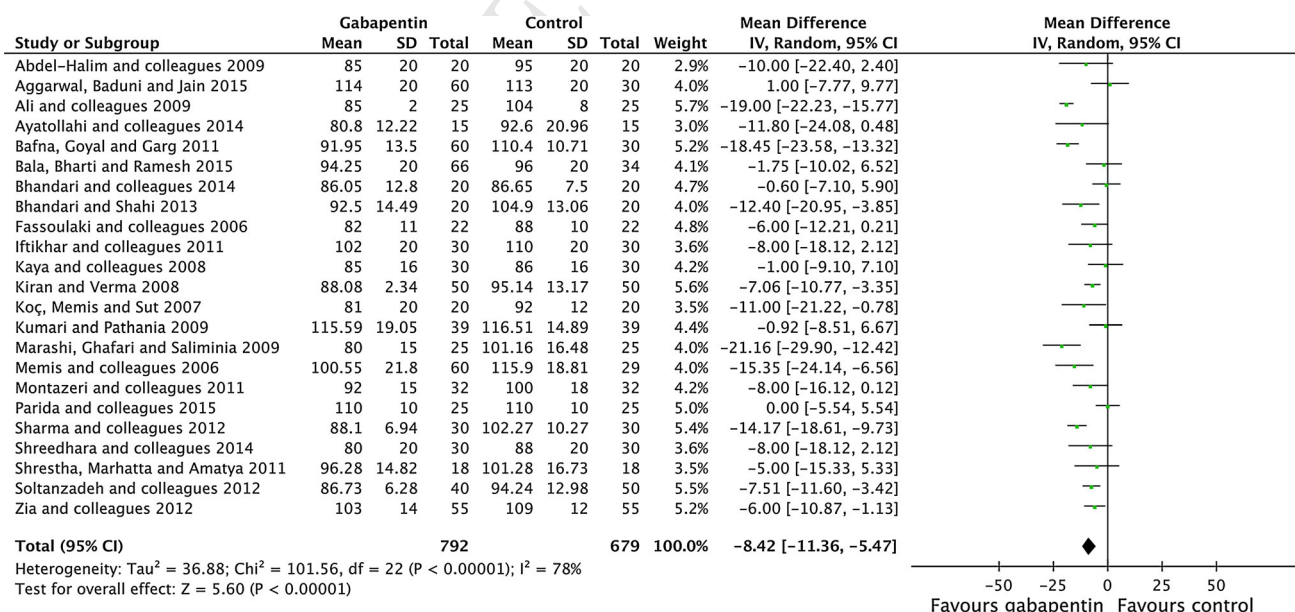

Fig. 4 Forest plot of gabapentin effects on heart rate at one minute

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

Other secondary outcomes

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

474 Gabapentin use reduced the incidence of hypertension or
475 tachycardia requiring treatment in five studies (RR, 0.15;
476 95% CI, 0.05 to 0.48; moderate quality). Trial sequential
477 analysis showed that gabapentin crossed the boundary for
478 benefit, although it did not reach the required information
479 size (558 participants). Definitions for this outcome were as
480 follows; SBP > 200 mmHg or > 30% increase from
481 baseline for more than 60 sec;[22,38] HR > 130 beats·min^{-1},
482 SBP > 200 mmHg or > 30% increase from baseline for
483 more than 60 sec;[26] MAP or HR >20% of baseline;[29] MAP
484 > 110 mmHg.[40]

485 One study[26] conducted in hypertensive patients reported
486 any incidences of hypotension requiring treatment (SBP <
487 90 mmHg or > 30% from baseline lasting more than 60
488 sec); there were no significant differences between the
489 groups (RR, 2.40; 95% CI, 0.74 to 7.79). One study[31]
490 reported any incidence of bradycardia requiring treatment
491 (HR< 40 beats·min^{-1}). There was no significant difference
492 in bradycardia with gabapentin (RR, 3.00; 95% CI, 0.13 to
493 69.87).

Gabapentin vs fentanyl, clonidine, or beta blockers

495 When compared with clonidine, the only significant
496 difference in hemodynamic variables was a higher HR at
497 ten minutes in the gabapentin group when compared with
498 the clonidine group[37,39,42-44] (MD, 5 beats·min^{-1}; 95% CI,
499 3 to 7; moderate quality). One study[45] compared
500 gabapentin with a beta blocker (esmolol). The only
501 difference in hemodynamic variables was a higher HR at
502 one minute in the gabapentin group when compared with
503 the esmolol group (MD, 13 beats·min^{-1}; 95% CI, 4 to 21).
504 The incidence of bradycardia was not significantly
505 different when gabapentin was compared with clonidine
506 (RR, 0.49; 95% CI, 0.07 to 3.60) or esmolol (RR, 0.33;
507 95% CI, 0.01 to 7.68).

508 One study compared gabapentin with intravenous
509 fentanyl.[41] Intravenous fentanyl resulted in greater

510 attenuation of HR at one (MD, 14 beats·min^{-1}; 95% CI,
511 8 to 20), five (MD, 12 beats·min^{-1}; 95% CI, 7 to 17), and
512 ten minutes (MD, 10 beats·min^{-1}; 95% CI, 5 to 15).
513 Furthermore, intravenous fentanyl resulted in greater
514 attenuation of MAP at one minute (MD, 13 mmHg; 95%
515 CI, 8 to 18).

Sensitivity analysis

517 Only two of the included studies were at low risk of
518 bias,[35,41] which resulted in no significant reductions for
519 many outcomes. Excluding studies with estimated standard
520 deviations did not significantly affect results. "Remove-
521 One" sensitivity analysis showed that there were no
522 influential studies in any of the analyses.

Discussion

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

542 With regard to outcome measurements, very few of the
543 included studies provided details of the equipment used to
544 obtain noninvasive blood pressure measurements. As
545 values from oscillometric methods are algorithmically
546 derived, these may vary between devices, which may
547 introduce heterogeneity into our results. Also, this lack of
548 information meant that it was problematic to evaluate
549 whether such devices are valid, precise, and accurate. As
550 the majority of the included studies measured blood
551 pressure at discrete time points, important hypotensive or
552 hypertensive episodes may have been missed, as such
553 discrete measurements may not reflect the average values
554 occurring between such measurements. Finally, it is
555 unclear how gabapentin compares with other standard
556 agents such as lidocaine. Importantly, when gabapentin
557 was directly compared with a standard agent such as

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

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,[63] 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.

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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