



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
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REVIEW ARTICLE

Perioperative gabapentin and pregabalin in cardiac surgery: a systematic review and meta-analysis



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Received 26 October 2015; accepted 20 July 2016

Available online 1 October 2016

KEYWORDS

Cardiac surgery;
Gabapentin;
Pregabalin;
Post-operative pain

Abstract

Objectives: Sternotomy for cardiac surgeries causes significant postoperative pain and when not properly managed may cause significant morbidity. As neuropathic pain is a significant component here, gabapentin and pregabalin may be effective in these patients and may reduce postoperative opioid consumption. The purpose of this systematic review was to find out efficacy of gabapentin and pregabalin in acute postoperative pain after cardiac surgery.

Methods: Published prospective human randomized clinical trials, which compared pre-operative and/or postoperative gabapentin/pregabalin with placebo or no treatment for postoperative pain management after cardiac surgery has been included in this review.

Results: Four RCTs each for gabapentin and pregabalin have been included in this systematic review. Three gabapentin and two pregabalin studies reported decrease in opioid consumption in cardiac surgical patients while one gabapentin and two pregabalin studies did not. Three RCTs each for gabapentin and pregabalin reported lower pain scores both during activity and rest. The drugs are not associated with any significant complications.

Conclusion: Despite lower pain scores in the postoperative period, there is insufficient evidence to recommend routine use of gabapentin and pregabalin to reduce opioid consumption in the cardiac surgical patients.

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PALAVRAS-CHAVE

Cirurgia cardíaca;
Gabapentina;
Pregabalina;
Dor no pós-operatório

Gabapentina e pregabalina no período perioperatório em cirurgia cardíaca: uma revisão sistemática e metanálise

Resumo

Objetivos: A esternotomia para cirurgias cardíacas causa dor intensa no pós-operatório e quando não tratada adequadamente pode causar morbidade grave. Como nesse caso a dor neuropática é uma componente importante, gabapentina e pregabalina podem ser eficazes

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nesses pacientes e podem reduzir o consumo de opioides no pós-operatório. O objetivo desta revisão sistemática foi avaliar a eficácia de gabapentina e pregabalina na dor aguda após cirurgia cardíaca.

Métodos: Estudos clínicos prospectivos e randômicos com humanos, que compararam o uso de gabapentina/pregabalina nos períodos pré- e/ou pós-operatório com placebo ou nenhum tratamento para o controle da dor no pós-operatório de cirurgia cardíaca foram incluídos nesta revisão.

Resultados: Quatro ECRs de gabapentina e pregabalina foram incluídos nesta revisão sistemática. Três estudos de gabapentina e dois de pregabalina relataram diminuição do consumo de opioides em pacientes cirúrgicos cardíacos; um estudo de gabapentina e dois de pregabalina não relataram. Três ECTs de gabapentina e pregabalina relataram escores menores de dor, durante a atividade e o repouso. Os medicamentos não estão associados a complicações significativas.

Conclusão: : Embora os escores de dor tenham sido menores no pós-operatório, não há evidências suficientes para recomendar o uso rotineiro de gabapentina e pregabalina para reduzir o consumo de opioides em pacientes cirúrgicos cardíacos.

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Introduction

Sternotomy for cardiac surgery causes significant postoperative pain,¹ which has both significant short term and long term consequences. Poorly managed acute postoperative pain may complicate immediate postoperative period^{2,3} and may also cause chronic pain.⁴ Though patients usually feel worst pain in the first postoperative day, significant pain may continue up to sixth postoperative day.⁵ Adequately managed acute pain lowers the myocardial oxygen demand and decreases the incidence of ischemic episodes.^{3,6} Parenteral opioids, though effective, may cause sedation, respiratory depression, nausea-vomiting and pruritus which may be troublesome.⁷ Moreover, opioids may have limited efficacy when pain is associated with activity such as coughing and deep breathing.⁸ Options of central neuraxial analgesia in cardiac surgical population is also limited mostly because of perioperative anticoagulant use, and its superiority to PCA opioid is also debatable.⁹

Acute postoperative pain may also have a significant neuropathic component along with nociceptive pain due to peripheral mechanoreceptor stimulation and both central and peripheral sensitization by several mechanisms.^{10,11} During sternotomy, intercostal nerves may be damaged by stretching of the intercostal nerves at the costo-vertebral junction due to sternal retraction and damage may also occur during dissection of internal mammary artery from the sternum; all of which ultimately contribute to neuropathic pain.

The gabapentinoids gabapentin and pregabalin are novel antiepileptic drugs, which also have significant efficacy in neuropathic pain^{12,13} and postoperative pain.^{14–16} They exert anti-nociceptive effect by binding with the $\alpha_2\delta$ subunit of voltage sensitive calcium channel.^{14,17} As well as having a central anti-allodynic effect they also inhibit pain transmission.¹⁷ The drugs are available only as oral preparations, and differ mainly in bioavailability. Gabapentin is absorbed in the duodenum by a saturable L-amino acid transport mechanism, so that bioavailability

varies inversely with dose.¹⁸ Bioavailability also varies widely between individuals underlining the need for dose individualization to achieve clinical goals.¹⁹ In contrast, pregabalin is absorbed throughout the small intestines with linear uptake without transporter saturation.¹⁷ Both the drugs have very low plasma protein binding, no metabolism and is excreted unchanged in urine; dose modification is needed in renal impairment.¹⁷ With an elimination half-life of 4.8–8.7 h, gabapentin requires thrice daily dosing.¹⁸ Altered formulations have been devised to facilitate once or twice daily regimens, e.g. Gralise (sustained release) and gabapentin enacarbil (a prodrug).²⁰ Pregabalin has an elimination half-life of 5.5–6.3 h, requiring twice to thrice daily dosing.¹⁷ Both are free from significant side effects and drug interactions in the clinically useful dosage.¹⁷ Gabapentin may be useful for the prevention of chronic postsurgical pain also.²¹ Both have also been extensively studied in various surgical population for postoperative pain management with varying degrees of success. Few RCTs^{22–29} have addressed the efficacy of perioperative administration of gabapentinoids on acute postoperative pain after cardiac surgery and they reported variable results. Hence, we conducted this systematic review to find out efficacy of gabapentin and pregabalin in acute postoperative pain after cardiac surgery.

Methods

Published prospective human clinical trials, which compared preoperative and/or postoperative gabapentin/pregabalin with placebo or no treatment for postoperative pain management after cardiac surgery has been included in this review.

Date source and search method

We did an electronic search in the following database: PubMed, PubMed Central, EMBASE and CENTRAL with the

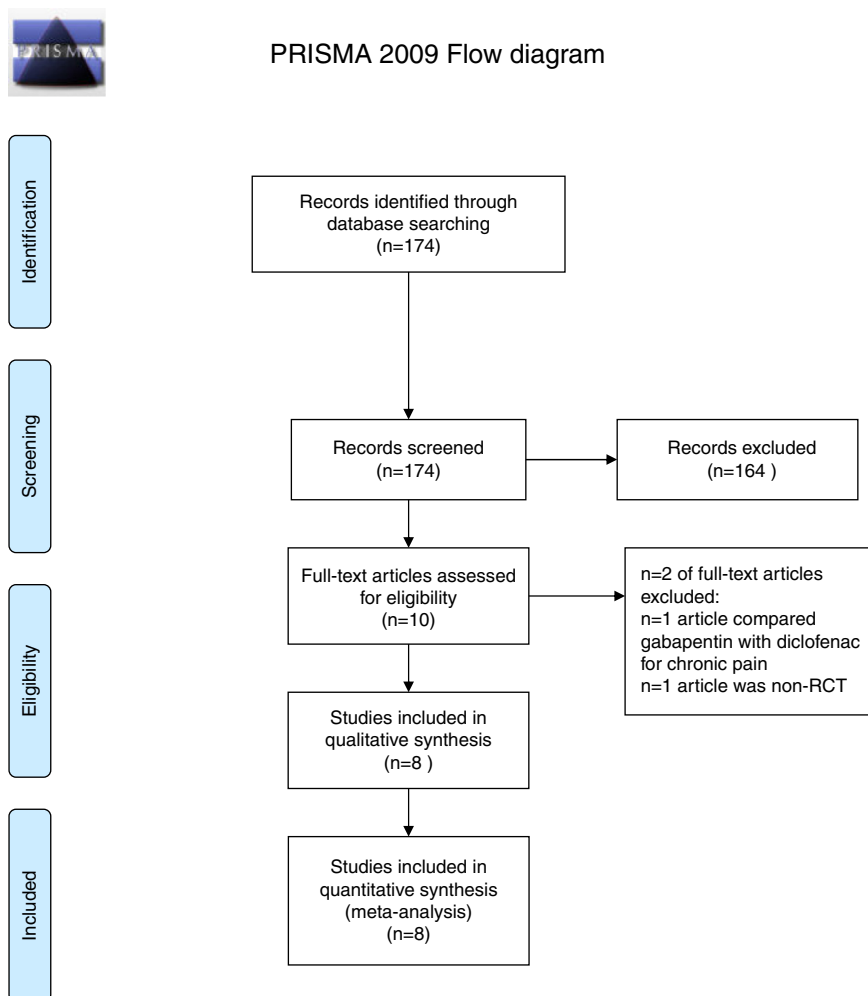


Figure 1 PRISMA flow diagram for study selection.

Keywords: “gabapentin”; “pregabalin”; “cardiac” and “sternotomy” to find out the eligible clinical trials on 20th September 2013. Another literature search was also done on 9th August; 2015 to update the result of the previous search. The search strategy in PubMed has been mentioned in [Appendix 1](#). References from the primary search results were also manually searched for potentially eligible trials.

Study selection

Published prospective randomized human clinical trials, which compared preoperative and/or postoperative gabapentin/pregabalin with placebo or no treatment for postoperative pain management after cardiac surgery have been included in this study. We did not impose any language restriction in the search strategy. Studies that have been done on either adult or pediatric population have been included in this review. We did not search for unpublished trials. Authors were not asked for unpublished data in the included trials. A PRISMA flow diagram³⁰ of study selection is depicted in [Fig. 1](#).

Exclusion criteria

Clinical trials where oral gabapentin or pregabalin has been compared with placebo or any other drug in surgical populations other than cardiac surgery were not included in this review. Studies which did not report the effects of the study drug on acute postoperative pain were also excluded. We also excluded studies where a postoperative regional analgesia technique was used as a part of multimodal regimen.

Data collection

Potentially eligible trials were manually searched from the abstracts to determine their eligibility in this review. We collected the required data from the full-text of the trials. Two authors independently (DKB, SB) extracted all data from the eligible trials. Initially all data were tabulated in Microsoft Excel™ spread sheet.

Data items

The following data were extracted from the eligible trials: Name of the first author, year of publication, methods of

randomization and blinding, study population, protocol of study drug administration, postoperative opioid consumption and pain scores, incidence of chronic pain following sternotomy and chronic pain scores, duration of mechanical ventilation and ICU stay, and adverse reactions. All the extracted data were tabulated in a Microsoft Excel spreadsheet.

Primary outcome measure of this review was postoperative pain scores (both at rest and dynamic). Secondary outcome measures were postoperative opioid consumption, effects of the study drugs on opioid related adverse effects, duration of mechanical ventilation and ICU stay.

Where a quantitative meta-analysis was not possible a qualitative systemic review of the reported data was performed.

Risk of bias in individual studies

The quality of eligible trials was assessed using the ‘risk of bias’ tool within Review Manager, version 5.2.3 software (Review Manager [RevMan]. Version 5.2. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012) by two authors working independently (SM and AS). Random sequence generation, allocation concealment, blinding, incomplete data, and selective reporting were assessed; based on the method of the trials, each was graded ‘yes’, ‘no’, or ‘unclear’, which reflected a high risk of bias, low risk of bias, and uncertain bias, respectively. Risks of bias summary in the individual studies have been provided in Fig. 2.

Results

Database searching revealed 174 articles. In six clinical studies gabapentin was used as an analgesic in cardiac surgeries. However, in one³¹ of them it was compared with diclofenac; hence it was excluded from analysis. Another RCT³² compared a gabapentin containing multimodal regimen with opioid-based analgesic regimen. Finally, four RCTs^{23,25,26,28} evaluating gabapentin and another four studying pregabalin^{22,24,27,29} met our inclusion criteria for this systematic review. Risk of bias in the individual studies has been furnished in Fig. 2. Study protocol of the individual studies and patient population have been described in Table 1. The pooled results have been summarized in the following section.

Postoperative pain

All the included studies reported pain scores at different points of time; hence a pooled analysis has not been possible.

Gabapentin

Ucak et al.²⁸ reported a lower pain score with the use of gabapentin both during rest and cough at 6 h, 12 h, 18 h, 24 h, 48 h and 72 h. Soltanzadeh et al.²⁶ reported that pain scores, both at rest and during coughing at 2 h, 6 h, and 12 h after extubation were significantly lower in patients who received gabapentin. Menda et al.²³ reported lower pain scores

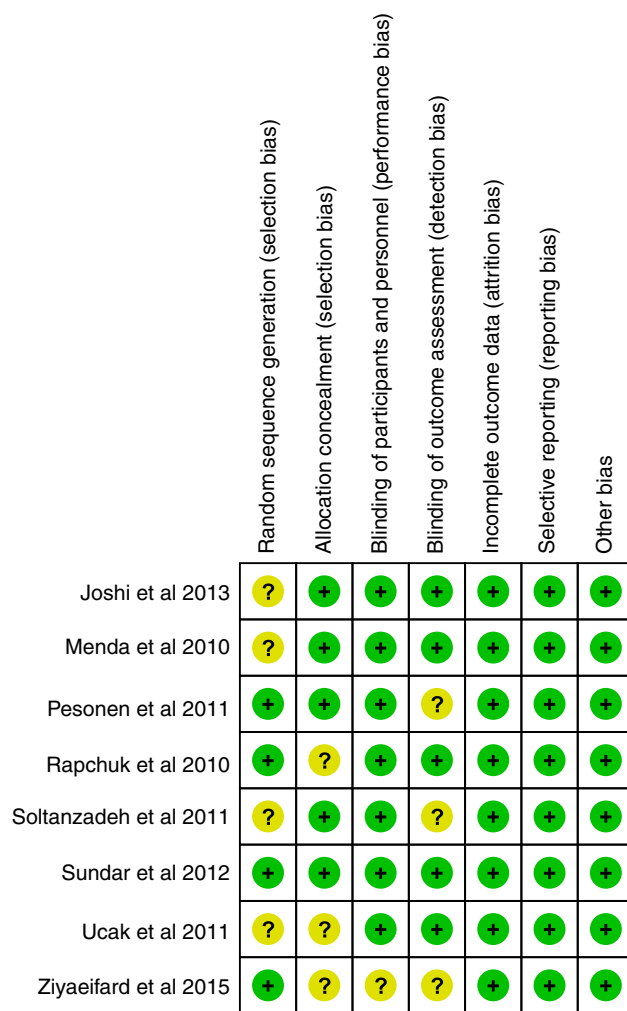


Figure 2 Summary of ‘‘risk of bias’’ at individual study level.

during rest up to 48 h after extubation but only up to 12 h for pain during coughing. However, Rapchuk et al.²⁵ reported a similar VAS score both during rest and coughing up to 72 h postoperative period. Rafiq et al.³² evaluated pain scores by 11 point NRS and found that patients in the gabapentin containing multimodal group, in all categories, except ‘‘worst pain’’ on day 4, had lower mean pain scores. Patients had significantly lower average pain sensation from day 0 (day of surgery) throughout to day 3. The least pain experienced during the day was also lower in the multimodal group from day 1 to day 3.

Pregabalin

In the study of Joshi et al.²² pain-scores at rest at 6 h, 12 h, 24 h and 36 h from extubation and pain scores at deep breath at 4 h, 6 h, 12 h, 24 h and 36 h from extubation were less in pregabalin treated patients ($p < 0.05$). They also found that peak inspiratory flow rates as assessed by incentive spirometry were higher in pregabalin group as compared to control group at 12 h, 24 h and 36 h from extubation ($p < 0.05$). Pesonen et al.²⁴ reported significantly lower percentage of patients requiring analgesia at 2 h, 10 h and 12 h after extubation in the pregabalin group ($p < 0.05$). Sundar et al.²⁷ could not detect any difference in VAS scores

Table 1 Summary of study protocol and results of individual studies.

Author & year	Patients	Study protocol	Post-operative analgesics	Analgesic outcome	Other outcome
<i>Gabapentin</i>					
Soltanzadeh M et al., 2011 ²⁶	60 men aged 20–70 years posted for CABG	Oral gabapentin 800 mg 2 h before surgery and 400 mg 2 h after extubation ($n = 30$), vs. placebo ($n = 30$)	Morphine	Pain scores both at rest and during coughing were significantly lower in the gabapentin group ($p = 0.02$). Hemodynamic changes (HR, SBP, DBP) and the incidence of nausea, vomiting and respiratory depression within 24 h were comparable between the two groups.	Postoperative mechanical ventilation was significantly ($p = 0.03$) longer (5.4 ± 1.7 h) in gabapentin than in control group (4.4 ± 1.6 h). The number of over-sedated patients (a sedation score > 2) was higher in gabapentin group.
Menda et al., 2010 ²³	60 young men undergoing CABG	Oral gabapentin 600 mg 2 h before surgery ($n = 30$), vs. placebo ($n = 30$)	Morphine PCA, paracetamol	Total morphine consumption was lower in the GABA group (6.7 ± 2.5) than the placebo (PLA) group (15.5 ± 4.6 mg, $p < 0.01$) at 24 h. Pain scores at rest were significantly lower in the GABA group throughout the study period ($p < 0.05$). Pain scores at 2, 6, and 12 h during coughing were significantly lower in the GABA group ($p < 0.05$), whereas pain scores during coughing were similar at 18, 24, and 48 h between the groups.	The postoperative mechanical ventilation period was significantly prolonged in the GABA group (6.6 ± 1.2 h) compared with the PLA group (5.5 ± 1 h, $p < 0.01$). The number of over sedated patients (patients with a Ramsay score > 2) was higher in the GABA group at 2, 6, and 12 h of study. There was lower incidence of nausea in the GABA group ($p = 0.02$).
Rapchuk et al., 2010 ²⁵	60 patients undergoing median sternotomy	Oral gabapentin 1200 mg 2 h before surgical incision and 600 mg twice a day for the next two postoperative days ($n = 30$), vs. placebo ($n = 30$).	Fentanyl PCA, paracetamol, tramadol, pethidine, NSAIDs	Total PCA fentanyl usage in the first 48 h was similar in two groups. VAS scores recorded at 12, 24, 48 and 72 h at rest and movement were not significantly different.	Sleep scores, number of antiemetic doses in first 48 h, adjunctive pain medications used and score achieved on the quality of recovery questionnaire were similar in the two groups. The incidence of side-effects (arrhythmias, dizziness and sedation) was also similar.

Table 1 (Continued)

Author & year	Patients	Study protocol	Post-operative analgesics	Analgesic outcome	Other outcome
Ucak A et al., 2011 ²⁸	40 patients with IHD undergoing CABG	Oral gabapentin 1.2 g·dL ⁻¹ 1 h before surgery and for 2 days after surgery (<i>n</i> = 20), vs. placebo (<i>n</i> = 20)	Tramadol, paracetamol	Postoperative pain scores at 1, 2, and 3 days were lower in the gabapentin group (<i>p</i> < 0.05). Pain scores at 1 and 3 months postoperatively were also lower in the gabapentin group (<i>p</i> > 0.05). Consumption of rescue analgesic (tramadol) within 24 h after extubation in the gabapentin group was 99.0 ± 53.8 mg vs. 149.4 ± 72.5 mg in the placebo group (<i>p</i> < 0.05).	There were no differences in the incidence of side effects and time to extubation.
<i>Pregabalin</i>					
Joshi et al., 2013 ²²	40 patients aged 30–65 years undergoing primary off-pump CABG	Oral pregabalin 150 mg 2 h before induction and 75 mg every 12 h for 2 post-operative days (<i>n</i> = 20), vs. placebo (<i>n</i> = 20)	Tramadol, paracetamol, diclofenac	Pain-scores at rest at 6, 12, 24 and 36 h from extubation and pain scores at deep breath at 4, 6, 12, 24 and 36 h from extubation were less in pregabalin treated patients (<i>p</i> < 0.05). Rescue analgesic (tramadol) consumption was reduced by 60% in pregabalin group (<i>p</i> < 0.001). The pain severity scores were higher in the control group at 12, 24 and 36 h (<i>p</i> < 0.05). Pain at rest and deep breathing at 1 month and 3 months after surgery were comparable among the groups.	Sedation (RASS), incidences of respiratory depression and nausea were comparable. Extubation time, duration of ICU and hospital stay were also similar. Peak inspiratory flow rates as assessed by incentive spirometry were higher in pregabalin group as compared to control group at 12, 24 and 36 h from extubation (<i>p</i> < 0.05)
Pesonen et al., 2011 ²⁴	70 patients aged 75 years or older, undergoing primary elective CABG or single valve repair or replacement with CPB	Oral pregabalin 150 mg 1 h before surgery and 75 mg twice daily for 5 postoperative days (<i>n</i> = 35), vs. placebo (<i>n</i> = 35)	Oxycodone	Percentage of patients requiring analgesia was significantly lower at 2, 10, and 12 h after extubation in the pregabalin group (<i>p</i> < 0.05).	RASS and MMSE scores were similar between the groups and CAM-ICU scores were significantly lower in the placebo group on the 1st postoperative day.

Table 1 (Continued)

Author & year	Patients	Study protocol	Post-operative analgesics	Analgesic outcome	Other outcome
Sundar et al., 2012 ²⁷	60 adult patients scheduled for elective off-pump CABG	Oral pregabalin 150 mg 1 h before surgery (<i>n</i> = 30), vs. placebo (<i>n</i> = 30)	Fentanyl	Pregabalin also reduced consumption of parenteral oxycodone during 16 h after extubation by 43% and total oxycodone consumption from extubation to the end of the fifth postoperative day by 48%. The incidence of pain during movement was significantly lower in the pregabalin group at 3 months postoperatively, but pain after 1 month was similar. VAS measured at 6, 12, and 24 h after surgery and fentanyl consumption up to 24 h after surgery was similar between the groups.	Time to extubation was significantly longer in the pregabalin group (638 ± 285 vs. 500 ± 233 min; <i>p</i> < 0.05). Incidence of nausea and vomiting was comparable. Ramsay sedation scores at 6, 12, and 24 h after surgery were similar between the groups. Duration of ventilation and ICU stay and incidences of nausea, vomiting and dizziness were also comparable. Duration of ICU stay was similar.
Ziyaeifard et al., 2015 ²⁹	60 patients older than 20 years posted for elective CABG	Oral pregabalin 150 mg 2 h before surgery (<i>n</i> = 30), vs. placebo (<i>n</i> = 30)	Morphine	Pain scores were significantly lower in the pregabalin group at 4, 12, and 24 h of surgery (<i>p</i> < 0.05); but morphine consumption was similar between the groups.	

CABG, Coronary Artery Bypass Grafting; HR, Heart Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; PCA, Patient Controlled Analgesia; IHD, Ischemic Heart Disease; ICU, Intensive Care Unit; VAS, Visual Analogue Scale; RASS, Richmond Agitation-Sedation Scale; MMSE, Mini Mental State Examination; CAM-ICU, Confusion Assessment Method for the ICU.

measured at 6 h, 12 h, and 24 h after surgery; while Ziyaeifard et al.²⁹ found pain scores to be significantly lower in the pregabalin group at 4 h, 12 h, and 24 h of surgery (*p* < 0.05).

Postoperative opioid consumption

Gabapentin

Three studies^{23,26,28} reported postoperative opioid consumption up to 24 h after extubation and one²⁵ reported fentanyl consumption up to 48 h. Two^{23,26} of them used morphine

and one²⁸ used tramadol. Menda et al.²³ found that pre-operative gabapentin reduces morphine consumption than placebo (6.7 ± 2.5 mg vs. 15.5 ± 4.6 mg, *p* < 0.01). Soltanzadeh et al.²⁶ reported pre and postoperative gabapentin reduces opioid consumption than placebo (0.9 ± 1.5 mg vs. 1.5 ± 4 mg, *p* = 0.01). Ucak et al.²⁸ reported intravenous tramadol consumption and found that gabapentin reduces tramadol consumption than placebo (99 ± 53.8 mg vs. 149.4 ± 72.5 mg, *p* < 0.05). Rapchuk et al.²⁵ reported similar fentanyl consumption at 48 h after extubation (1355 ± 995 mcg vs. 1562 ± 1056 mcg; *p* = 0.46; *n* = 54).

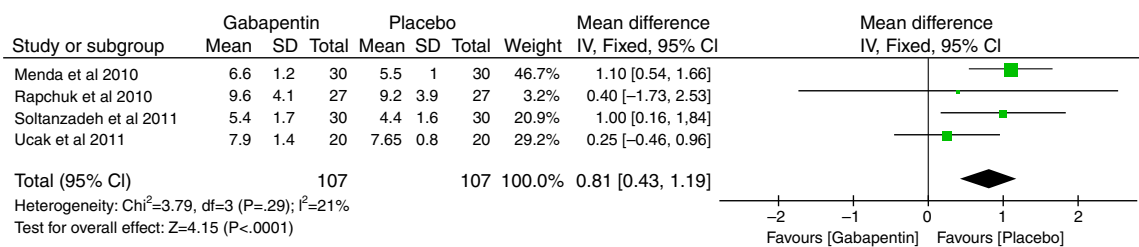


Figure 3 Forest plot showing pooled analysis of mean difference of duration of mechanical ventilation for gabapentin.

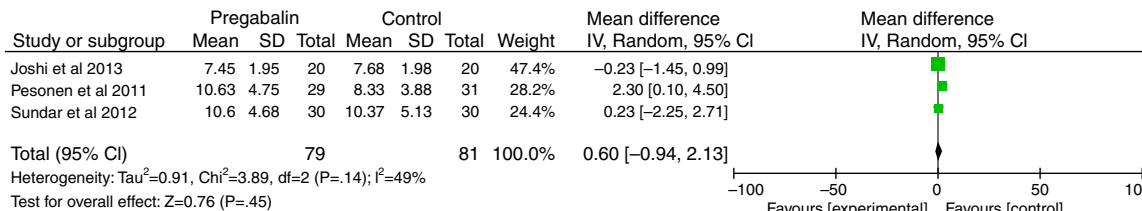


Figure 4 Forest plot showing pooled analysis of mean difference of duration of mechanical ventilation for pregabalin.

Pregabalin

Joshi et al.²² found that tramadol consumption was reduced by 60% in the pregabalin group compared to placebo (67.8 ± 60.25 mg vs. 167.1 ± 52.1 mg, $p < 0.001$). Pesonen et al.²⁴ reported that pregabalin reduced consumption of parenteral oxycodone during 16 h after extubation by 43% (8 ± 5 mg vs. 14 ± 6 mg, $p < 0.001$) and total oxycodone consumption from extubation to the end of the fifth postoperative day by 48% (48 ± 28 mg vs. 93 ± 44 mg, $p < 0.001$). However, Sundar et al.²⁷ and Ziyaeifard et al.²⁹ found no difference in fentanyl (241.67 ± 178.87 mcg vs. 251.67 ± 181.47 mcg, $p > 0.05$) and morphine (3 ± 0.17 mg vs. 3.1 ± 0.15 mg, $p > 0.05$) consumption up to 24 h after surgery respectively. Of note, pregabalin was continued in the postoperative period in the first two RCTs (till days 2 and 5 respectively),^{22,24} and was used as a single preoperative dose in the last two.^{27,29}

Chronic pain

Gabapentin

Ucak et al.²⁸ found that pain scores at 1 and 3 months postoperatively were lower in the gabapentin group but the difference was not statistically significant ($p > 0.05$).

Pregabalin

In the study by Joshi et al.²² pain at rest and deep breathing at 1 month and 3 months after surgery were comparable among the groups. Pesonen et al.²⁴ reported that the incidence of pain during movement was significantly lower in the pregabalin group at 3 months postoperatively, but pain after 1 month was similar.

Duration of mechanical ventilation

A pooled analysis found that duration of mechanical ventilation is significantly increased with the use gabapentin (MD = 0.81 h; 95% CI 0.43–1.19; $p < 0.0001$; $n = 214$) (Fig. 3)

but not with pregabalin (MD = 0.60 h; 95% CI -0.94–2.13; $p = 0.45$; $n = 160$) (Fig. 4).

Length of ICU stay

Use of perioperative gabapentin (MD = 1.06 h; 95% CI -0.67–2.79; $p = 0.23$; $n = 120$) or pregabalin (MD = 0.63 h; 95% CI -3.59–4.85; $p = 0.77$; $n = 220$) does not affect the duration of ICU stay significantly.

Postoperative complications

Gabapentin

Commonly reported adverse effects of gabapentin are sedation, dizziness and somnolence.¹⁷ Ucak et al.²⁸ reported no increased incidence of any of the adverse effects of gabapentin. Menda et al.²³ reported an increased incidence of sedation (Ramsay sedation score > 2) with the use of gabapentin at 2 h, 6 h and 12 h after extubation. They also reported a significantly less incidence of nausea in gabapentin treated patients. Rapchuk et al.²⁵ and Soltanzadeh et al.²⁶ also reported no increased adverse effect with the use of gabapentin.

Pregabalin

Pregabalin has a side effect profile similar to that of gabapentin.¹⁷ Sedation scores and incidence of nausea/vomiting as reported by three RCTs^{22,24,27} were comparable between groups. Joshi et al.²² also reported similar incidence of respiratory depression and Sundar et al.²⁷ found similar occurrence of dizziness between the groups. On the other hand, CAM-ICU scores were significantly lower in the placebo group on the 1st postoperative day in the study of Pesonen et al.²⁴

Discussion

The principal findings of this review are that gabapentin did not reduce postoperative opioid consumption after cardiac surgery; but may reduce pain scores at the expense of increased duration of mechanical ventilation. However, gabapentin was safe and free of serious adverse effects and a single study²³ reported decreased incidence of nausea also. Pregabalin, on the other hand, decreased postoperative pain scores; reduced opioid consumption when it was continued in the postoperative period; and did not increase duration of mechanical ventilation, sedation or other side effects.

Efficacy of perioperative gabapentin in reducing pain is well established in other surgeries like spine surgeries,³³ breast surgeries,³⁴ gynecologic surgeries³⁵ etc. However, it may not have efficacy in management of post craniotomy pain.³⁶ It is likely that gabapentin will be more effective where neuropathic component is significant. Futility of single preoperative dose of gabapentin has been found in various settings.³⁷⁻³⁹ Gabapentin may be more effective in postoperative pain management at higher doses and when administered both pre and postoperatively.¹⁷ Amongst the included studies in our review, Ucak et al.²⁸ and Rapchuk et al.²⁵ used gabapentin at a dose of 1200 mg·day⁻¹ 2 h before surgery and continued in the postoperative period also. However, Menda et al.²³ used only in the preoperative period and Soltanzadeh et al.²⁶ used a lower dose of gabapentin (800 mg·day⁻¹). It is notable that despite using gabapentin at a dose of 1200 mcg·day⁻¹ both pre and postoperatively, Rapchuk et al.²⁵ did not find any reduction of pain scores and fentanyl consumption. Parlow et al.⁴⁰ in 2010 found that plasma concentration of gabapentin is unaffected by cardio-pulmonary bypass and patients who received gabapentin consume similar amount of morphine in the postoperative period as those who did not. In previous studies,⁴¹ where gabapentin was found to be ineffective, use of regional anesthesia in those studies was blamed and a speculation was made that regional anesthesia could have prevented central sensitization. However, none of the studies included here used any regional anesthesia technique. From a clinical point of view, a reduced opioid requirement may be more important than only pain scores. Again pain scores recorded at specific time points only does not imply patients' analgesia over a time period. None of the studies reported patients' satisfaction level here.

Data reporting chronic pain was inadequate for any conclusion.

Efficacy of pregabalin in reducing post-operative acute pain has been reviewed in several meta-analyses.^{15,42,43} Eipe et al.¹⁵ came to the conclusion that pregabalin decreases analgesic consumption following various types of surgeries, but had a small effect in improving pain control and this effect is primarily observed in surgeries associated with pronociceptive mechanisms, e.g. spine, joint arthroplasty, and amputations. As sternotomy and sternal retraction involves intercostal nerve damage and associated central and peripheral sensitization, acute allodynia and hyperalgesia often occur.¹⁰ This may explain the finding of reduced pain scores with pregabalin in three of the included RCTs.^{22,24,29} Two RCTs^{22,24} which had continued pregabalin 150 mg·day⁻¹ in the postoperative period, demonstrated reduced opioid consumption, whereas the

other two RCTs^{27,29} using single preoperative 150 mg dose of pregabalin did not find any reduction. In the case of Sundar et al.,²⁷ their study was not adequately powered to detect differences in pain scores or opioid consumption. The absence of effect in the other one²⁹ corroborates the conclusion of Schmidt et al.¹⁷ that continuing the drug postoperatively is likely to be more effective than a single preoperative dose, though it is in contrast to the finding by Mishriky et al. in their meta-analysis.⁴² Mishriky et al.⁴² had found no significant difference between single and multiple dosing regimens, but their analysis had a significant component of heterogeneity because of pooling of different surgeries and anesthesia techniques. This contradiction calls for further research in this area. However, it should be noted that the effect of cardio-pulmonary bypass on pregabalin has not been studied. In at least one study,²² improved analgesia translated into improved peak inspiratory flow rates as assessed by incentive spirometry.

Increased duration of mechanical ventilation after gabapentin use may be due to a well-known side effect of gabapentin i.e. increased sedation. However, the increment is clinically insignificant: mean difference is only 0.81 h (48 min). It is to be kept in mind that the studies used different extubation and weaning protocol and this result is to be interpreted cautiously. Pregabalin did not increase duration of mechanical ventilation. Both drugs did not have any effect on the duration of ICU stay.

Despite popular belief, gabapentin was shown to increase sedation in one RCT only. None of the studies reported any serious adverse effects of gabapentin. Moreover, one study²³ found that gabapentin may reduce postoperative nausea also. It is not surprising, because it may have similar efficacy after craniotomy also.³⁶ A lower morphine requirement in gabapentin treated patients may be responsible for this. Incidences of sedation, respiratory depression and nausea/vomiting were not altered with pregabalin as well. This lack of significant side effects may be explained by the use of a lower dose (150 mg) of the drug.

The clinical relevance of our review is that in spite of small individual studies reporting benefit of using perioperative gabapentinoids in cardiac surgery, our analysis failed to corroborate any unambiguous clinical efficacy, though no significant adverse effect is associated. So, there is no strong evidence to support using perioperative gabapentin and pregabalin in cardiac surgical patients at this time.

Limitations

The most important limitation of our review is the inclusion of limited number of studies. Despite extensive database searching, only eight studies could be included. Individual studies, though well designed, comprise small number of patients. A large RCT in the future may alter our finding. The dosage protocols of gabapentin and pregabalin are also varied in the studies. Data on chronic pain is also very limited.

Conclusion

At this time there is insufficient evidence to recommend routine use of gabapentin and pregabalin to reduce opioid

consumption in the cardiac surgical patients primarily for the management of acute postoperative pain.

Conflicts of interest

The authors declare no conflicts of interest.

Appendix 1.

(“gabapentin” [Supplementary Concept] OR “gabapentin” [All Fields]) AND (“heart” [MeSH Terms] OR “heart” [All Fields] OR “cardiac” [All Fields])
 (“gabapentin” [Supplementary Concept] OR “gabapentin” [All Fields]) AND (“sternotomy” [MeSH Terms] OR “sternotomy” [All Fields])
 (“pregabalin” [Supplementary Concept] OR “pregabalin” [All Fields]) AND (“heart” [MeSH Terms] OR “heart” [All Fields] OR “cardiac” [All Fields])
 (“pregabalin” [Supplementary Concept] OR “pregabalin” [All Fields]) AND (“sternotomy” [MeSH Terms] OR “sternotomy” [All Fields])

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