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Impact of pregabalin on acute and persistent postoperative pain: a systematic review and meta-analysis

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Editor's key points

- The authors reviewed the evidence for the use of pregabalin for pain relief in the perioperative period.
- They found a significant positive effect (in terms of improved pain scores, opioid-sparing and reduction in nausea, vomiting, and pruritus), but a slight increase in some side-effects.

Summary. We performed this systematic review to assess the analgesic efficacy of perioperative pregabalin. Subgroup analyses and meta-regression were performed to assess the impact of individual dose and frequency of pregabalin administration on analgesic efficacy. We included 55 studies. When all doses and administration regimens were combined, pregabalin was associated with a significant reduction in pain scores at rest and during movement and opioid consumption at 24 h compared with placebo {mean difference [95% confidence interval (CI)]=−0.38 (−0.57, −0.20), −0.47 (−0.76, −0.18), and −8.27 mg morphine equivalents (−10.08, −6.47), respectively}. Patients receiving pregabalin had less postoperative nausea and vomiting and pruritus compared with placebo [relative risk (RR) (95% CI)=0.62 (0.48, 0.80) and 0.49 (0.34, 0.70), respectively]. Sedation, dizziness, and visual disturbance were more common with pregabalin compared with placebo [RR (95% CI)=1.46 (1.08, 1.98), 1.33 (1.07, 1.64), and 3.52 (2.05, 6.04), respectively]. All doses of pregabalin tested (≤75, 100–150, and 300 mg) resulted in opioid sparing at 24 h after surgery. There were no significant differences in acute pain outcomes with pregabalin 100–300 mg between single preoperative dosing regimens and those including additional doses repeated after surgery. Data were insufficient to reach conclusions regarding persistent pain, but limited data available from two studies suggested that pregabalin might be effective for the reduction of neuropathic pain. In conclusion, this review suggests that pregabalin improves postoperative analgesia compared with placebo at the expense of increased sedation and visual disturbances.

Keywords: meta-analysis; postoperative pain; pregabalin

Pregabalin is a γ-aminobutyric acid analogue that binds to $\alpha_2\delta$ subunits of the voltage-gated calcium channels.[1] It reduces the excitability of the dorsal horn neurones after tissue damage.[2] The use of pregabalin for the management of postoperative pain is off-label, and therefore, there are no dosing guidelines for this indication. For other indications, the recommended starting dose is 150 mg day^{-1} in two to three divided doses, increased within 1 week to 300 mg day^{-1} with a maximum recommended dose of 600 mg day^{-1}.[2] Studies investigating the perioperative use of pregabalin used doses ranging from 50 to 300 mg and daily doses ranging from 50 to 750 mg. The efficacy of perioperative administration of pregabalin was investigated in previous meta-analyses,[3–5] with all showing better postoperative analgesia with pregabalin. Those meta-analyses grouped studies based on the total daily dose of pregabalin. Zhang and colleagues[5] reported that pregabalin doses of <300 and ≥300 mg day^{-1} reduced 24 h opioid consumption but not pain scores after surgery. Engelman and Cateloy[4] grouped the analysis over a wide time-frame (6 h–7 days after surgery) according to the daily dose of pregabalin (50–150, 225–300, and 600–750 mg) and reported that the lowest effective dose for reducing postoperative analgesic consumption was 225–300 mg with no reduction in pain scores. Since doses were reported in those meta-analyses as total daily dose, it is not clear if the individual dose or frequency of administration of pregabalin affect outcome. For instance, it is not clear from those reviews if individual single doses lower than 225–300 mg have analgesic efficacy or if twice daily dosing of a particular dose of pregabalin would be more effective than single preoperative administration of the same dose. Some studies have investigated the impact of pregabalin on preoperative anxiety, but this was not addressed in those previous meta-analyses. More than 30 studies investigating perioperative pregabalin administration on acute pain outcomes have been published after the publication of those reviews, which included 11[5] and 18[4] studies. In addition, while one previous meta-analysis[3] assessed the impact of the perioperative administration of pregabalin on chronic pain, it included only three studies.[6–8] Seven other studies[9–15] addressing persistent pain after pregabalin administration have since been published.

Therefore, we performed this systematic review to provide an updated meta-analysis of the impact of pregabalin administration on postoperative pain scores and opioid consumption and investigate whether those outcomes differ according to individual pregabalin dose, frequency of administration, type

of anaesthesia, or type of surgery. Secondary aims were to assess the impact of pregabalin administration on anxiety scores and persistent pain, and provide an updated meta-analysis of the side-effects of pregabalin administration.

Methods

We followed the recommendations of the PRISMA statement.[16]

We searched MEDLINE (1966–2014), the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE (1947–2014), and CINAHL for randomized controlled trials (RCTs) that compared pregabalin with control in patients undergoing surgery. Databases were searched using the term 'pregabalin' combined with the MESH terms: 'Pain, postoperative', 'Postoperative period', 'Pain, acute', 'Pain, chronic', 'Opioids', and 'Analgesics, opioid'. The search was performed without language restriction. The last literature search was done on March 31, 2014. We also searched the bibliographies of retrieved articles for additional studies. Reviews, abstracts, letters to the editor, and retrospective studies were not included. Articles were included if pregabalin was administered before operation and pain scores, opioid consumption, incidence of persistent pain, and/or time to first analgesia were reported. We excluded studies where pregabalin administration was initiated after operation, the endpoints of interest were not reported or if a placebo group was not included.

The articles meeting the inclusion criteria were assessed separately by two authors (B.M.M. and N.H.W.) using the risk of bias table suggested by the Cochrane Collaboration.[17] A data collection sheet was created and two authors (B.M.M. and N.H.W.) extracted data on:

(i) Patients: type of surgery, type of anaesthesia, and number of patients.
(ii) Interventions: pregabalin dose and frequency of administration.
(iii) Comparison: control group regimen.
(iv) Outcomes: (a) acute pain outcomes: pain scores at rest and during movement, opioid consumption, and duration of post-anaesthesia care unit (PACU) and hospital stay, (b) preoperative anxiety scores, (c) adverse effects: nausea, vomiting, sedation, dizziness, confusion, headache, visual disturbance, pruritus, difficulty passing urine, dry mouth, fatigue, and request for rescue antiemetics, and (d) persistent pain: pain scores and incidence of persistent pain.

Data presented in graphs were requested from the authors. If authors did not respond, data were extracted from the graph. Discrepancies between the two authors were resolved by discussion with the third author (A.S.H.).

The primary outcomes of this meta-analysis were pain scores and opioid consumption at 2 and 24 h. Secondary outcomes were duration of PACU and hospital stay, incidence of persistent pain at 1, 3, 6, and 12 months, preoperative anxiety scores, and side-effects.

Analyses performed for the research questions and synthesis of data

Acute pain outcomes

In studies involving different doses of pregabalin, we combined all pregabalin doses for the main analysis assessing the impact of pregabalin administration on postoperative pain scores and opioid consumption. Visual analogue scale (VAS) scores for pain reported as 0–100 was converted to the 0–10 scale for analysis (0, no pain; 10, worst possible pain). Opioids were converted to morphine equivalents (ME) for analysis using a conversion factor of 3:1 for oxycodone,[18] 0.15:1 for parenteral hydromorphone,[18] 10:1 for fentanyl,[18] 20:1 for codeine,[18] 10:1 for tramadol,[5] and 1:1 for both ketobemidone[19] and piritramide.[20] If ketorolac was the only analgesic used, it was converted to ME using a conversion factor of 3:1.[21] If results were not reported at the time points specified in this analysis, those recorded close to those time points were used instead.

To evaluate different pregabalin dosing regimens, we performed subgroup analyses for pain scores and opioid consumption at 2 h after operation according to the individual dose of pregabalin administered before surgery ($\leq$75, 100–150, and 300 mg). For pain scores and opioid consumption at 24 h, we performed a subgroup analysis according to the dose and frequency of administration of pregabalin comparing the three dose levels ($\leq$75, 100–150, and 300 mg) and single *vs* multiple dosing at each dose level. Single dosing refers to studies that administered a single preoperative dose of pregabalin, while multiple dosing refers to studies that used at least one postoperative dose of pregabalin in addition to the preoperative dose or administered more than one preoperative dose. We also performed sensitivity analyses according to the type of surgery and type of anaesthesia (general *vs* regional) for the primary outcomes of pain scores and opioid consumption at 2 and 24 h. To evaluate predictors that could impact our primary outcomes, we also performed a meta-regression using pregabalin dose, type of surgery, and type of anaesthesia (general or regional) as predictors for the 2 h outcomes. The frequency of administration of pregabalin (single *vs* multiple dosing) was used as an additional predictor for 24 h outcomes.

Preoperative anxiety

We pooled preoperative anxiety scores after administration of pregabalin compared with placebo. VAS scores for anxiety reported as 0–100 were converted to the 0–10 scale for analysis.

Side-effects of perioperative pregabalin administration

We pooled adverse effects after administration of pregabalin compared with placebo. If an event rate was reported over multiple time intervals instead of the entire duration of the study, the highest recorded incidence over the duration of the study was used in the analysis. Sedation was defined as scores 3–6 on the Ramsay sedation scale (1, patient is anxious and agitated or restless; 2, patient is co-operative,