Regional Anesthesia and Pain

Preoperative gabapentin for postoperative analgesia: a meta-analysis

[L'administration préopératoire de gabapentine pour l'analgésie postopératoire: une méta-analyse]

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Purpose: Gabapentin's role in the treatment of chronic neuropathic pain is well known. What is less well established is its role for managing postoperative pain. In order to clarify whether gabapentin's utility in acute pain control is more than just theoretical, we conducted a meta-analysis of all randomized trials that addressed gabapentin's role in acute postoperative pain control. We specifically addressed whether gabapentin reduces pain scores, analgesia consumption, and/or analgesia-related side effects in the first 24 hr following surgery.

Source: We identified eight placebo-controlled, randomized controlled trials and conducted a meta-analysis using the primary outcomes of pain scores, total analgesia consumption, and side effects over a 24-hr period.

Principle findings: Patients who received gabapentin preoperatively reported significantly lower pain scores (-11.9 at rest and -11.0 with movement on a 100-point visual analogue scale) and opioid consumption (-14.7 mg of morphine in 24 hr) with no difference in the incidence of side effects.

Conclusion: Although gabapentin given preoperatively decreases pain scores and analgesic consumption in the first 24 hr after surgery, the clinical significance of this finding has yet to be determined. This meta-analysis could not demonstrate a significant reduction in the incidence of side effects. Due to the small numbers enrolled in the studies, larger randomized control trials are warranted.

***Objectif** : Le rôle de la gabapentine dans le traitement de la douleur neuropathique chronique est bien connu. Ce qui l'est moins, c'est son rôle dans le traitement de la douleur postopératoire. Pour le vérifier, nous avons fait une méta-analyse de toutes les études randomisées qui ont abordé le rôle de la gabapentine dans le contrôle de la douleur postopératoire aiguë. Nous avons surtout cherché si la gabapentine réduit les scores de douleur, la consommation d'analgésique et/ou les effets secondaires reliés à l'analgésie des 24 premières heures postopératoires.*

***Source** : Nous avons repéré huit études randomisées, contrôlées contre placebo et mené une méta-analyse en utilisant les principaux paramètres des scores de douleur, consommation totale d'analgésique et effets secondaires pendant 24 h.*

***Constatations principales** : Les patients qui ont reçu de la gabapentine préopératoire ont présenté des scores de douleur (-11,9 au repos et -11,0 au mouvement sur une échelle visuelle analogique de 100 points) et une consommation d'opioïdes (-14,7 mg de morphine en 24 h) significativement plus faibles, mais une incidence d'effets secondaires similaire.*

***Conclusion** : Quoique la gabapentine donnée avant l'opération diminue les scores de douleur et la consommation d'analgésique pendant les 24 premières heures postopératoires, la portée clinique de ce résultat reste indéterminée. Cette méta-analyse ne peut démontrer de réduction significative d'incidence des effets secondaires. Étant donné les petits échantillons étudiés, de plus grandes études randomisées et contrôlées sont nécessaires.*

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THE literature examining the efficacy of preoperative administration of analgesic medications for the management of acute postoperative pain has been controversial. Non-steroidal anti-inflammatory drugs, local anesthetics, alpha$_2$ agonists and N-methyl-D-aspartate receptor antagonists are the main drug groups which have been investigated for their synergistic role with opioid analgesics in the management of postoperative pain. Recently, Gilron *et al.* demonstrated a synergistic effect of gapabentin with morphine in the setting of chronic neuropathic pain.[1] Gabapentin may also work synergistically with opioids in the treatment of postoperative pain. Although its use in treating chronic neuropathic pain has been established, gabapentin has not been the subject of a meta-analysis to evaluate its potential efficacy as an adjunctive analgesic.

Introduced in 1994 as an anti-epileptic drug, gabapentin soon found promise in the treatment of neuropathic pain associated with postherpetic neuralgia,[2,3] diabetic neuropathy[4] and cancer pain,[5] among other chronic pain states. Its usefulness in the context of chronic neuropathic pain (i.e., when pain response is amplified and allodynia is present)[6] suggests it may have a role in the prevention of postoperative allodynia. Its side effect profile is favourable in comparison to other anti-convulsants, yet it remains to be seen whether dizziness and somnolence caused by gabapentin in the treatment of neuropathic pain might limit its use as an adjunct in acute pain management, should its utility in that domain ever be demonstrated.

The mechanism of action of gabapentin remains unresolved. Various laboratory investigations have suggested that while gabapentin does not affect nociceptive thresholds, it may have a selective effect on the nociceptive process involving central sensitization.[7] It was Woolf who first implicated the role of central neuronal sensitization in the amplification of postoperative pain.[8] Subsequent studies in animal models of incisional and thermal injury have shown that systemic or intrathecal gabapentin reduces hyperalgesia[9,10] and enhances the anti-nociceptive effect of morphine.[11] Similar results were demonstrated in healthy human volunteers, in whom gabapentin enhanced the effect of morphine,[12] and reduced secondary hyperalgesia.[13]

While the laboratory evidence points to a promising role of gabapentin in acute pain management, data derived from clinical reports and studies have been less conclusive. Although several randomized controlled trials have attempted to evaluate whether the preemptive use of gabapentin reduces postoperative pain scores, opioid consumption and/or side effects, these trials have been small and the results, although tending to favour gabapentin, are somewhat conflicting. To date, no single, sufficiently large randomized controlled trial evaluating gabapentin as an adjunct to postoperative acute pain therapy has been conducted. A meta-analysis is therefore needed to ascertain if there is a role for gabapentin as an adjunctive analgesic medication and to establish directions for future trials. If the use of gabapentin in concert with opioid analgesics can be shown to control pain better than opioids alone – or equally, but with a better side effect profile – then gains may be realized in terms of more rapid patient mobilization, shorter hospital stays, and improved patient satisfaction.

In order to clarify gabapentin's potential efficacy in acute pain control, we conducted a meta-analysis of all randomized trials evaluating gabapentin's role in acute postoperative pain control. We specifically sought to determine whether gabapentin reduces pain scores, analgesic consumption, and/or analgesia-related side effects in the first 24 hr following surgery.

Methods

Study identification

Trials were identified by several methods. Randomized trials of gabapentin in acute pain control following surgery were identified by MEDLINE from 1966 to December 2004, EMBASE 1980 to December 2004, CINAHL, and the Cochrane Controlled Trials Register (CCTR). We combined the sensitive search strategy developed by Haynes *et al.* for identifying clinical trials in MEDLINE,[14] with free text combinations, including the following search themes: gabapentin; pain; postoperative pain; pain measurement; postoperative nausea and vomiting; postoperative care; postoperative analgesia; postoperative period. The reference lists of selected studies and review articles were reviewed for additional citations. No language restrictions were applied. Unpublished studies were not sought.

Study selection

Eligibility was determined by reading each abstract identified by the search. All reports were read by both authors and agreement was reached by consensus. The reports were not anonymized in any way prior to assessment. Inclusion criteria were established *a priori* and were as follows:

1. Population

The studies included in this review enrolled male and female patients over the age of 18 who underwent elective or non-elective surgical treatment resulting in the need for acute postoperative pain control for at least 24 hr.

2. INTERVENTION

Included studies compared the analgesic effects of adjunctive gabapentin *vs* placebo on acute postoperative pain and analgesia consumption. Gabapentin dosing consisted of single or multiple dose regimens, where the first dose was given preoperatively. Studies were excluded if the intervention was targeted primarily towards a chronic pain condition. Postoperative analgesia consisted of opioid or non-opioid agents, administered by nurse or patient controlled analgesia (PCA).

3. OUTCOME

The outcomes under analysis were total analgesic consumption during the period under observation, reductions in pain scores at rest or on mobilization, and side effects, particularly nausea, vomiting and sedation.

4. METHODOLOGY

Included studies were prospective controlled trials randomized to gabapentin *vs* a control arm. Cohort studies, case reports, observational studies and experimental models were excluded. Randomized control trials were included regardless of quality assessment or results.

Study evaluation

The internal validity of the included studies was assessed independently by each author. A modified form of the five-point methodological quality scale designed by Jadad *et al.*[15] was used to score each study. High methodological quality was indicated by a high score and reflected appropriate methods of randomization and concealment of allocation. Specifically, studies that were described as being randomized and double-blind, that demonstrated completeness of follow-up, used appropriate methods to generate the randomization sequence and described the blinding method – which was appropriate – received full points. Where studies were not described as randomized, randomization was inferred if neither the patient nor the assessors of the study outcomes could identify the treatment group to which the patients belonged. Completeness of follow-up was taken to mean that a description of withdrawals and dropouts was given, or alternatively, all of the registered patients were accounted for in the results. This last point represented a small modification of the original scale where completeness of follow-up must be explicitly stated. This modification was employed because of the short-term nature of perioperative pain studies whereby completeness of follow-up can easily be discerned from the number of patients in the Results *vs* the Methods section.

Data extraction

Each author independently extracted data from each study. Information on the patients, intervention and outcome were recorded on data sheets. Data extracted included contact information, study design, type of surgery, type of anesthetic, anesthetic drugs, number of subjects in each treatment group, subject demographic variables and baseline characteristics, regimen and dose of gabapentin treatment, type and method of delivery of postoperative analgesia, postoperative monitoring intervals, type and severity of side effects, the mean visual analogue scale scores and whether the scores were recorded at rest or on movement, mean analgesic consumption, number of subjects accounted for in results, and if the authors of the study advocated gabapentin for adjunctive analgesia.

A priori hypothesis regarding sources of heterogeneity

Prior to analyzing the results, a number of hypotheses were made to explain any heterogeneity in the effect size of pain, analgesic or side effect reduction between studies.

First, the severity of pain is influenced by the type of surgery performed. Some surgeries (e.g., spinal surgery and hysterectomy) are more invasive than others (e.g., laparoscopic cholecystectomy), and hence prone to more painful recoveries. Gabapentin may have a more appreciable effect in a study where the nature of the surgery predisposes to a difficult recovery in the first place. Second, the dose and regimen of gabapentin was not the same in all studies. Any inconsistency across studies in the magnitude of gabapentin's treatment effect may therefore be a function of different dosing and regimens. Third, the type of outcome data collected for side effects may influence whether one treatment was found to have a more favourable side effect profile over another. For example, a study reporting side effects as a dichotomous outcome might not detect a difference in results, whereas a study reporting side effects as continuous data might.

Analysis

Three outcomes were analyzed including total analgesic consumption, pain scores and side effects. The analysis was based on the treatment effect for each individual study and a random effects model generated by Review Manager was used (The Cochrane Collaboration, 4.2.7, 2004).

For dichotomous data, such as side effects, fractions of patients experiencing the outcome were collected or derived, in order to calculate the odds ratio for outcome. For continuous data, the mean value ± the standard deviation was recorded for each treatment

TABLE Description of studies

Reference	*No. of patients/ surgery*	*Methodology/ intervention*	*Gabapentin dosing regimen*	*Primary analgesic*	*Outcome measures*
Dierking *et al.*, 2004 [21]	80 Abdominal hysterectomy	RCT Gabapentin or placebo	1 hr before surgery 1200 mg gabapentin; 8, 16, 24 hr after initial dose: 600 mg	PCA morphine	•Pain scores at rest & on mobilization •Incidence of side effects •Morphine consumption •Gabapentin plasma levels
Dirks *et al.*, 2002 [23]	70 Mastectomy	RCT Gabapentin or placebo	1 hr before surgery 1200 mg gabapentin	PCA morphine	•Pain scores at rest & on mobilization •Incidence of side effects •Morphine consumption
Fassoulaki *et al.*, 2002 [19]	67 Radical mastectomy & lumpectomy	RCT Gabapentin, mexiletine or placebo	400 mg gabapentin or 200 mg mexiletine tid beginning the night before surgery × 10 day	*im* paracetamol, propoxyphene and codeine.	•Pain scores at rest & on mobilization •Analgesia consumption •Time to first analgesic requirement
Pandey *et al.*, 2004 [18]	459 Lap cholecystectomy	RCT Gabapentin, tramadol or placebo	2 hr before surgery 300 mg gabapentin or 100 mg tramadol	*iv* fentanyl on demand	•Pain scores at rest •Incidence of side effects •Fentanyl consumption •Preop anxiety
Pandey *et al.*, 2004 [25]	56 Lumbar discoidectomy	RCT Gabapentin or placebo	2 hr before surgery 300 mg gabapentin	*iv* fentanyl on demand	•Pain scores •Incidence of side effects •Fentanyl consumption
Rorarius *et al.*, 2004 [17]	75 Vaginal hysterectomy	RCT Gabapentin or oxazepam	2.5 hr prior to surgery 1200 mg gabapentin or 15 mg oxazepam	PCA fentanyl	•Pain scores at rest •Incidence of side effects •Fentanyl consumption
Turan *et al.*, 2004 [22]	50 Spinal surgery	RCT Gabapentin or placebo	1 hr before surgery 1200 mg gabapentin	PCA morphine	•Pain scores •Incidence of side effects •Morphine consumption
Turan *et al.*, 2004 [24]	50 Abdominal hysterectomy	RCT Gabapentin or placebo	1 hr before surgery 1200 mg gabapentin	PCA tramadol	•Sitting and supine pain scores •Incidence of side effects •Tramadol consumption. •Postop HR, MAP and RR

RCT = randomized controlled trials; PCA = patient controlled analgesia; HR = heart rate; MAP = mean arterial pressure; RR = respiratory rate.

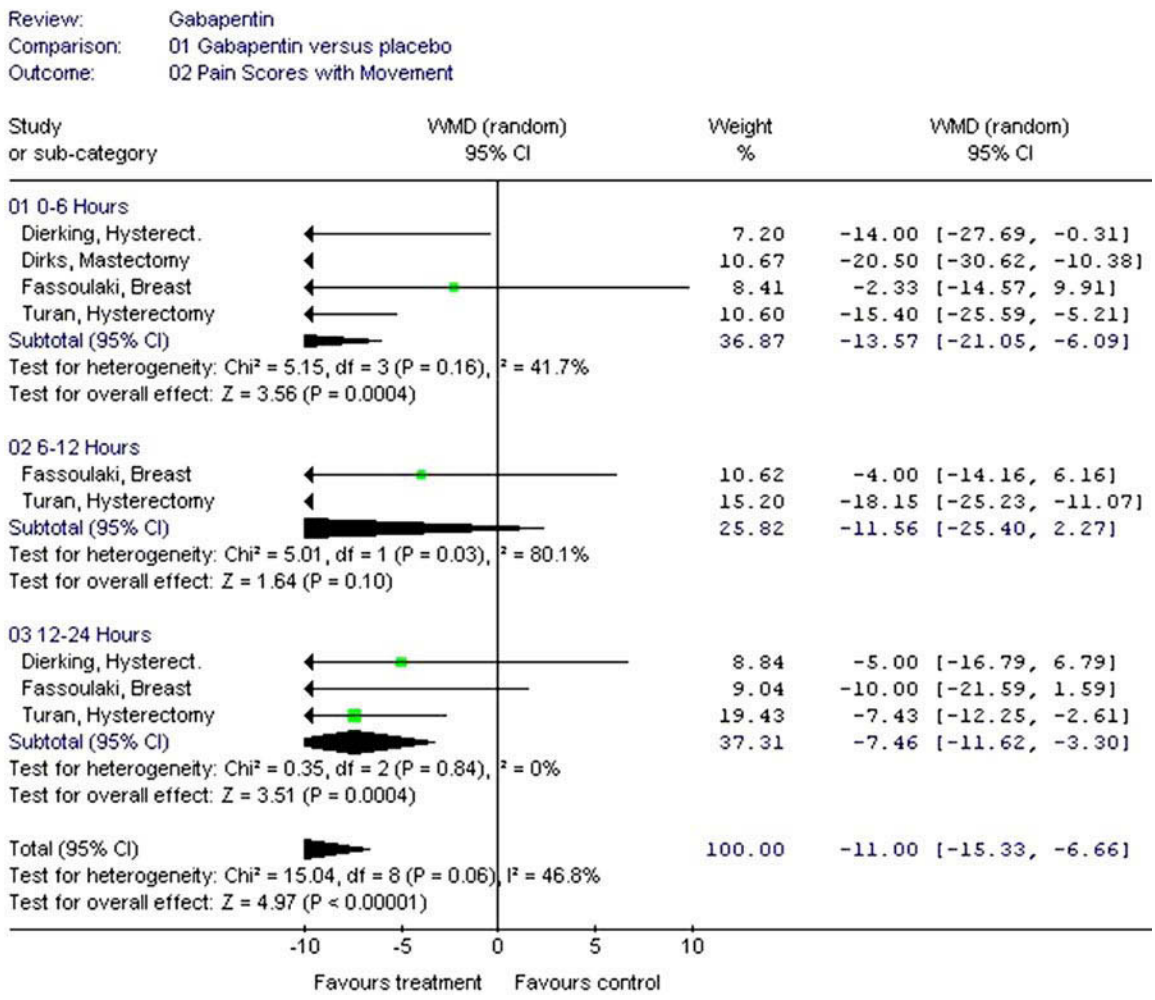

FIGURE 1 Pain scores (visual analogue scale 0–100) with movement at 0–6, 6–12 and 12–24 hr after surgery.

group. When standard deviations were not given, they were calculated from the interquartile range (standard deviation = ¾ × interquartile range).

The randomized control trials used a variety of time intervals for pain assessment. For the purpose of comparing pain scores across different time intervals, we grouped time intervals into a standard set (0–6 hr; 6–12 hr; 12–18 hr; 18–24 hr). Visual analogue scores were reported out of 10 and 100. For the analysis, all scores were converted to a 100-mm scale. For the purposes of comparing postoperative analgesic consumption, we converted all postoperative opioid analgesic boluses to their morphine equivalent using equianalgesic tables for opioid equivalency.[16] We compared the total opioid consumption over a period of 24 hr, although some studies recorded data for a shorter period, and some for a longer period.

All studies that continued gabapentin in the postoperative period were analyzed[17,18] to determine if the treatment effect was more pronounced with multiple dosing. Since the study by Fassoulaki *et al.*[19] did not evaluate side effects, only pain scores and analgesia consumption were submitted for analysis.

Results

After excluding a number of reports as obvious reviews or experimental reports in humans or animals, the computerized database searches yielded a total of nine potentially eligible articles. Eight met the inclusion criteria. The other article was excluded because it was unpublished and could not be obtained (even after several attempts to contact the author).[20] The details of these studies and the quality scores are presented in the Table. The overall quality of the articles

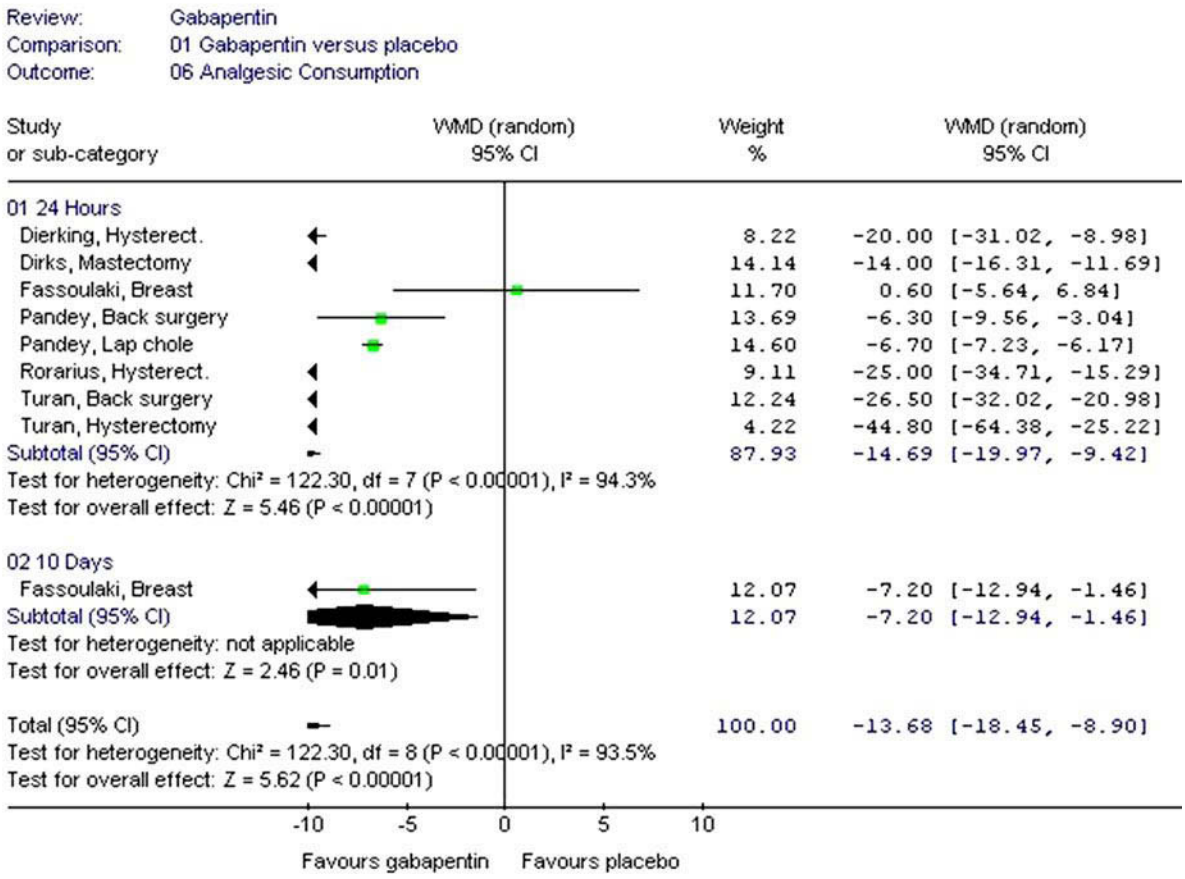

FIGURE 2 Analgesic consumption at 24 hr and ten days after surgery.

was very good, with six of the eight articles having a quality score of 5/5 and the remaining two having scores of 3 and 4, respectively.

The eight eligible studies contained information on a total of 663 subjects, 333 of whom received gabapentin, and 330 of whom were controls. Of the 333 patients who received gabapentin, 62 received multiple dosing,[19,21] and the rest received single doses prior to surgery. The surgeries included abdominal hysterectomy,[21,22] radical mastectomy or lumpectomy,[19,23] vaginal hysterectomy,[17] laparoscopic cholecystectomy[18] and lumbar discectomy or spinal fusion.[24,25] Due to the nature of the surgeries, four of the trials evaluated female patients only. One study did not evaluate side effects.[19] Given the similarity of the interventions (gabapentin plus opioids), populations (postsurgical pain) and outcomes (pain scores, analgesia consumption, and side effects) we chose to combine the results into a meta-analysis. Specific outcomes were as follows:

Pain scores

Five of the eight studies showed statistically significant ($P < 0.05$) lower pain scores at rest in the gabapentin groups [weighted mean differences (WMD) 11.9; 95% confidence interval (CI) 8.4–15.5], (Figure A, available as Additional Material at www.cja-jca.org).[17,18,22,24,25] This difference was most pronounced at 12–18 hr postoperatively. While the study by Fassoulaki *et al.*,[19] which measured pain at rest as well as pain on mobilization, found no significant difference in visual analogue scale scores at rest during the first 24 hr postoperatively, it did find significantly lower resting pain scores in the gabapentin group by the third postoperative day. In addition, Fassoulaki *et al.*[19] found significantly lower pain scores on mobilization in the gabapentin group from the second through fifth postoperative days.

All studies which evaluated pain scores on mobilization[19,21–23] showed a statistically significant reduction in pain scores during the first 24 hr postoperatively (WMD 11.0; 95% CI 6.7–15.3), (Figure 1).

The meta-analysis demonstrated that the use of gabapentin was associated with lower postoperative pain scores, with this difference being particularly pronounced at 12–18 hr postoperatively (WMD 15.9; 95% CI 7.1–24.7), (Figure A, available as Additional Material at www.cja-jca.org). This difference was also found in favour of gabapentin for pain on mobilization.

Analgesic consumption

All but the study by Fassoulaki *et al.*[19] found lower opioid consumption ($P < 0.05$) in the gabapentin treatment arm (WMD 13.7; 95% CI 8.9–18.5), (Figure 2). Fassoulaki *et al.*'s[19] study did not show a reduction in analgesic consumption in the first 24 hr, however, it did find that opioid consumption was halved in the gabapentin group from the second to tenth postoperative days ($P < 0.05$).

Adverse effects

Dichotomous data on adverse effects were available in all but the study by Fassoulaki *et al.*[19] The incidence of gabapentin-related side effects (dizziness, light headedness, visual disturbance and headache) was similar in the gabapentin and control groups (Figure B, available as Additional Material at www.cja-jca.org). Similarly, there were no significant differences with respect to the incidence of opioid related adverse effects (nausea, vomiting, sedation, constipation, urinary retention, pruritis, and respiratory depression) between the gabapentin and control groups.

Multiple dosing effect

A sensitivity analysis of the only two studies[17,18] to use postoperative dosing of gabapentin was conducted to assess whether multiple dosing resulted in a more pronounced treatment effect. Results showed no significant difference in pain scores at rest (WMD 1.7; 95% CI 4.8–1.4) or upon mobilization (WMD 6.6; 95% CI 1.3–11.8). Although analgesic consumption was reduced, the difference was not significant (WMD 5.7; 95% CI 1.2–9.7).

Discussion

We identified eight randomized controlled trials that compared gabapentin to placebo as an adjunctive analgesic for postoperative pain. Only six of these eight studies examined a single dose preoperatively. Five of the studies as well as our pooled analysis demonstrated statistically significant lower pain scores at rest in all time intervals for the first 24 hr postoperatively, with use of gabapentin administered preoperatively. This reduction in pain is greatest between 12 and 18 hr. There was no clear tapering of effect over time.

The differences in pain scores on mobilization were more modest, but this estimate was made on a smaller subset of patients (252 of the 663 patients in the review). The pattern appeared to support a tapering of effect over time, with reduction in pain scores with mobilization highest amongst the gabapentin-treated patients between zero to six hours postoperatively.

Our meta-analysis showed that there was a higher overall analgesic consumption in the control arm, despite equivalent pain scores. One study demonstrated significant difference in analgesic consumption only when consumption was assessed beyond 24 hr postoperatively, suggesting that a reduction in analgesic consumption may occur beyond the first 24 hr postoperatively.

Pain scores are problematic in a study where pain is controlled with PCA, since by its very design PCA allows patients to avoid escalating pain. Therefore, in a study designed with PCA for rescue analgesia, pain scores may be very similar between two treatment groups. The most important primary outcome therefore is total analgesic consumption.[26] A second useful outcome is that of time to first rescue analgesia – an outcome not measured in most of the studies included in this meta-analysis. Prolonging the time to first analgesic request means, in theory at least, that the duration of analgesia has been increased without increasing the dosage or dosing frequency. This, in turn, could result in less pain, less total analgesic consumption, and better patient satisfaction.[27] Therefore, future randomized control trials might find more conclusive evidence of gabapentin's efficacy as preemptive analgesia, if time to first analgesia were considered.

With respect to pain scores, a study by Farrar *et al.* suggested that a minimum 33% cut-off point is required before a clinically important difference in pain scores is identified.[28] If this cut-off point is used, our 12 mm reduction in pain scores is of debatable clinical value. Given its short half-life, the key to more important clinical improvement might lie in multiple doses of gabapentin, rather than a single preoperative dose.

Three studies did not find significantly lower pain scores. Of these, two involved mastectomies, suggesting that gabapentin may be effective an adjunctive analgesia in some surgeries and not others. Surgery with low-intensity noxious stimuli during primary and secondary phases of injury may not generate enough difference between the preoperative administration and control groups. As a result, postoperative pain will represent only "nociceptive," not "neuropathic" pain. In the absence of pathologic pain, preemptive

analgesia has nothing to prevent.[6] However, given the small number of studies included in this meta-analysis, no sensitivity analysis based on the type of surgery was possible.

When taken together, the reductions in pain scores and analgesic consumption would seem to predict a lower incidence of opioid-related side effects in the gabapentin arm with still adequate analgesia. However, analysis of side effects between the two treatment arms did not yield this observation convincingly. Despite less use of opioid analgesics, there was no significant difference overall in the incidence of opioid-related side effects between gabapentin and placebo. However, small numbers of patients result in low event rates; a larger group of patients would need to be studied before significant differences in adverse effects between the two treatment groups could be identified. Gabapentin has its own side effect profile of dizziness, somnolence and nausea, and these might offset any potential improvements in opioid-related side effects.

The dose of gabapentin did not appear to have any overall bearing on the outcomes. Dosing ranged from 300 mg to 1200 mg preoperatively. The studies which evaluated the lowest doses yielded the least impressive reductions in analgesic consumption,[18,19,25] but otherwise there were no appreciable differences in results based upon dosing. It is worthwhile noting that gabapentin is currently not available parenterally, which may limit its utility among those for whom the oral route is not an option.

Based on the sensitivity analysis of the studies which had multiple dosing regimens, our results did not show that continuing gabapentin treatment into the postoperative period conferred any additional benefit in the first 24 hr after surgery. However, these results represented a small number of patients from only two studies. Further studies are required before firm conclusions can be made regarding the effect of postoperative dosing.

Conclusions

From this meta-analysis it is reasonable to conclude that when given preoperatively, gabapentin is effective in reducing postoperative opioid consumption (WMD 13.7; 95% CI 8.9–18.5) in the first 24 hr after surgery and, to a lesser extent, reducing pain scores (WMD 11.9; 95% CI 8.4–15.5; WMD 11.0; 95% CI 6.7–15.3 for pain at rest and with mobilization, respectively). Dosing may play a role, with doses of 1200 mg being more effective in reducing analgesic consumption than doses of 300 or 400 mg. Despite reducing opioid consumption, gabapentin treatment did not reduce the incidence of opioid related side effects. Larger studies are required to determine if gabapentin may confer any benefit in reducing the incidence of postoperative nausea and vomiting or other side effects. Randomized controlled trials are required to quantify the dose-response relationship for efficacy and adverse effects. Further studies are also warranted to determine if continuing gabapentin into the postoperative period offers any benefit over a single preoperative dose.

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