Use of gabapentin for perioperative pain control: a meta-analysis

Peng P W, Wijeysundera D N, Li C C

CRD summary
This generally well-conducted review assessed the use of gabapentin for peri-operative pain control in adults. The authors concluded that gabapentin is associated with a reduction in pain, analgesic consumption and opioid-related side-effects, but there is an increased risk of dizziness and sedation. These conclusions appear to be supported by the data presented, although there may be some risk of publication bias.

Authors' objectives
To assess the analgesic effectiveness, opioid-sparing effects and side-effects of gabapentin used peri-operatively.

Searching
MEDLINE (1966 to February 2006), EMBASE (1980 to February 2006), the Cochrane Controlled Trials Register (Issue 1, 2006), Science Citation Index, Current Controlled Trials Register, TextMed, Science Direct, IngentaConnect and Google Scholar were searched for studies published in any language; the search terms were reported. The bibliographies of included articles and published reviews were also screened. Abstracts were excluded and unpublished studies were not sought.

Study selection
Study designs of evaluations included in the review
Studies of parallel-group randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of gabapentin used pre-operatively (within 24 hours), intra-operatively or post-operatively (within 24 hours) were eligible for inclusion. Studies including a local anaesthetic technique or nerve block were excluded. Most of the included studies used 1,200 mg/day gabapentin; other doses ranged from 300 mg/day to 1,800 mg/day. The majority of studies administered a single dose of gabapentin 1 to 2 hours before surgery, while the remaining studies administered the drug the day before surgery or up to 10 days after surgery. One study used a control arm of oxazepam 15 mg, whilst the remaining studies compared gabapentin with placebo.

Participants included in the review
Studies of adults (aged at least 18 years) undergoing surgery and receiving general anaesthetic, regional anaesthetic or monitored anaesthesia care were eligible for inclusion. The participants in the included studies were aged from 29 to 52 years and the proportion of females ranged from 32 to 100%. The surgical procedures studied included abdominal or vaginal hysterectomy, laparoscopic cholecystectomy, open nephrectomy, and knee, spine, lower limb, breast or major orthopaedic surgery.

Outcomes assessed in the review
Studies of cumulative analgesic consumption (24 hours), visual analogue scale (VAS) pain scores or adverse effects (dizziness, sedation, respiratory depression, nausea, vomiting, pruritus or urinary retention) were eligible for inclusion. The follow-up periods ranged from 4 to 72 hours.

How were decisions on the relevance of primary studies made?
Three reviewers independently searched for and selected studies for inclusion.

Assessment of study quality
Three reviewers independently assessed the quality of the included trials, with any disagreements resolved by consensus. The authors rated studies according to adequacy of randomisation, allocation concealment, double-blinding and whether drop-outs were accounted for, and awarded each study a score from 0 to 5 points using the Jadad scale.

Data extraction
Two reviewers extracted the data. The authors did not state whether this was performed independently. Study authors were contacted for further data where necessary. For dichotomous variables, the number of events in each group was extracted and used to calculate the relative risk (RR) with 95% confidence interval (CI). Cumulative analgesic consumption over 24 hours was extracted as the ratio of mean analgesic use in the gabapentin arm compared with the control arm. Means and standard deviations (SDs) were extracted for time to first analgesic and absolute reduction in pain VAS.

**Methods of synthesis**
How were the studies combined?
The results from the studies were combined in a meta-analysis, using a fixed-effect model where no heterogeneity was present and a random-effects model where there was evidence of statistical heterogeneity. Pooled RRs, ratios of means and weighted mean differences (WMDs) were reported, along with corresponding 95% CIs. Publication bias was assessed using funnel plots.

How were differences between studies investigated?
The I-squared statistic was used to assess statistical heterogeneity. Sensitivity analyses were conducted separately for high-quality studies and studies showing severe post-operative pain (more than 30 mm at rest in the control arm).

**Results of the review**
Eighteen studies (n=1,181) met the inclusion criteria.

Thirteen studies achieved the maximum Jadad score of 5. Eighty-nine per cent of studies fulfilled the quality criteria of describing the randomisation method and double-blinding. Seventy-eight per cent accounted for drop-outs, but only 56% reported adequate allocation concealment.

Gabapentin was associated with a 35% reduction in analgesic use in the first 24 hours post-operatively (ratio of means 0.65, 95% CI: 0.59, 0.72, p<0.001). However, there was evidence of significant heterogeneity (I-squared 84.4%), which was not accounted for by surgical procedure, dosage or study quality. Gabapentin delayed time to first analgesic by 7.9 minutes (WMD 7.9, 95% CI: 4.2, 11.6, p<0.001). There was no evidence of statistical heterogeneity.

Gabapentin significantly reduced pain by 27% (95% CI: 6.8 mm, 15.8 mm) at rest 2 hours post-operatively and by 39% (95% CI: 8.5 mm, 20.2 mm) at rest 4 hours post-operatively. This reduction in pain was maintained at 12 and 24 hours post-operatively. However, there was evidence of statistical heterogeneity in measurements at 12 hours (I-squared 73.9%) and 24 hours (I-squared 64.7%). With the exception of 24 hours after surgery, gabapentin use was also associated with a significant reduction in pain with movement, ranging from 18 to 28% after surgery. There was, however, evidence of significant heterogeneity in the 12 hour post-operative measurements (I-squared 71.9%).

Gabapentin was associated with a significantly increased risk of dizziness (RR 1.40, 95% CI: 1.06, 1.84, p<0.02) and a decreased risk of pruritus (RR 0.30, 95% CI: 0.13, 0.70, p<0.005) and vomiting (RR 0.73, 95% CI: 0.56, 0.95, p<0.02). There was no evidence of statistical heterogeneity for these analyses. There was also a borderline increased risk of sedation with gabapentin (RR 1.65, 95% CI: 1.00, 2.74, p=0.05), although there was evidence of significant heterogeneity in this analysis (I-squared 83.3%). The use of gabapentin did not have a significant impact on the occurrence of respiratory depression or nausea.

The results of the review did not change when only high-quality studies or studies with severe post-operative pain were included.

There was no evidence of publication bias.

**Authors’ conclusions**
Gabapentin improves the analgesic efficacy of opioids at rest and with movement, reduces analgesic consumption and reduces opioid-related adverse events. However, it is also associated with an increased risk of dizziness and sedation.

**CRD commentary**
The inclusion criteria were clear and well-defined. Several relevant databases were searched and steps were taken to minimise language bias. Unpublished articles do not appear to have been sought. The authors reported that they used funnel plots to assess publication bias but did not find any evidence of obvious bias. Appropriate steps were taken to minimise error and bias in the study selection and validity assessment processes. Given the presence of significant statistical heterogeneity for some outcomes, the review would have benefited from further information about individual the studies in a narrative synthesis. This was a generally well-conducted study and the authors’ conclusions appear to be supported by the data presented, though there may be some risk of publication bias.

**Implications of the review for practice and research**

*Practice:* Physicians should be cautious about the potential for sedation and dizziness in ambulatory surgical patients.

*Research:* Further research is needed to examine the effects of gabapentin on mechanical hyperalgesia on or around the wound post-operatively and anxiety using well-validated assessment tools. Future studies should assess the optimal dosage of gabapentin and include a more detailed assessment of the frequency and severity of adverse events.

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