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Dr John P Williams
Division of Medical Sciences and Graduate Entry Medicine
University of Nottingham
Royal Derby Hospital
Uttoxeter Road
Derby
DE22 3DT
Telephone: 01332 724641
Fax: 01332 724697

A systematic review and meta-regression analysis of prophylactic gabapentin for postoperative pain

B. Doleman,¹ T.P. Heinink,¹ D. Read,¹ R. J. Faleiro,² J. N. Lund³ and J. P. Williams⁴

1 Research Fellow, 2 Consultant Anaesthetist, Royal Derby Hospital, Derby, UK

3 Associate Professor and Honorary Consultant, Department of Surgery, 4 Associate Professor and Honorary Consultant, Department of Anaesthesia, University of Nottingham, Derby, UK

Correspondence to: Dr John P Williams: john.williams7@nottingham.ac.uk

Short title: Gabapentin for postoperative pain

Summary

We searched MEDLINE, Embase, CINAHL, AMED and CENTRAL databases to December 2014 and included 133 randomised controlled trials of peri-operative gabapentin vs. placebo. Gabapentin reduced mean (95% CI) 24 h morphine-equivalent consumption by 8.44 (7.26-9.62) mg, $p < 0.001$. Gabapentin effect was largely predicted ($R^2 = 90\%$, $p < 0.001$) by the meta-regression equation: $3.73 + (-0.378 \times \text{control morphine consumption (mg)}) + (-0.0023 \times \text{gabapentin dose (mg)}) + (-1.917 \times \text{anaesthetic type})$, where 'anaesthetic type' is '1' for general anaesthesia and '0' subarachnoid anaesthesia. The type of surgery was not independently associated with gabapentin effect. Gabapentin reduced postoperative pain scores on a ten-point scale at 1, 2, 6, 12 and 24 h by a mean (95% CI) of: 1.68 (1.35-2.01); 1.21 (0.88-1.55); 1.28 (0.98-1.57); 1.12 (0.91-1.33); and 0.71 (0.56-0.87), $p < 0.001$ for all. Gabapentin reduced postoperative nausea, vomiting and pruritus, but increased sedation: risk ratios (95% CI): 0.78 (0.69-0.87); 0.67 (0.59-0.76); 0.64 (0.51-0.80); and 1.18 (1.09-1.28), $p < 0.001$ for all. Gabapentin reduced pre-operative anxiety and increased patient satisfaction on a ten-point scale by a mean (95% CI) of 1.52 (0.78-2.26) points and 0.89 (0.22-1.57) points, $p < 0.001$ and $p = 0.01$, respectively. Gabapentin may be less effective due to publication bias, suggested by statistically significant small study effects.

Introduction

Most patients have postoperative pain and in 10% it is severe [1]. Analgesia provided by opioids and non-steroidal anti-inflammatory drugs may be supplemented by other drugs, such as gabapentin. Gabapentin is probably analgesic through its inhibition of calcium influx to A δ and C neurons, reducing excitatory neurotransmitter release from the dorsal horn and thereby inhibiting nociception [2-4].

Gabapentin reduces pain in chronic neuropathic states [5]. Peri-operative gabapentin reduces postoperative pain, opioid consumption, pruritus, nausea and vomiting [6-11]. However, the effects of gabapentin in the randomised controlled trials included by meta-analyses have been heterogeneous. Different operations cause different types and severities of pain and it has been suggested that the effects of analgesics depend upon the type of surgery [12, 13]. Few meta-analyses of postoperative pain have formally analysed the independent association of analgesic effect with type of surgery and only 8% assessed small study effects [12, 14-16]. The presence of small study effects and the possibility of publication bias should weaken the conclusions of systematic reviews and associated recommendations [17].

We aimed to systematically review the effects of gabapentin on postoperative outcomes and explore sources of heterogeneity and small study effects.

Methods

We used recommended methods for this prospectively-registered systematic review [18]. One author (BD) searched MEDLINE, Embase, CINAHL, AMED and CENTRAL to December 2014 with ‘gabapentin’, ‘neurontin’, ‘surgery’ and the exploded MeSH subject heading ‘Surgical procedures, operative’. We searched retrieved trials and Google Scholar for additional references. We contacted authors for unpublished data and registrants of unpublished trials at Clinicaltrials.gov and the ISRCTN registry [19].

We included placebo-controlled trials of any dose of gabapentin given before the end of any type of surgery, with or without subsequent doses. We used Google Translate for trials that were not written in English. We excluded trials of children (< 16 years old) and combination therapies. Two authors (BD and JW) agreed whether to include or exclude trials that they had independently evaluated.

The primary outcome was 24 h morphine-equivalent consumption. The secondary outcomes were postoperative pain scores at rest, recorded < 1 or at 2, 6, 12 and 24 h after surgery. We included ‘postoperative day one’ pain scores in the 24 h outcome. Pain scores averaged over defined time periods were analysed at the latest time point reported. We also evaluated chronic pain as a continuous outcome at 1-2, 3, 6 and 12 months. We considered a 10 mg reduction in morphine consumption and a 1.5 unit reduction in pain score clinically significant [20]. We converted opioids to morphine equivalents with the following ratios: pethidine 10:1; ketobemidone 1:1; tramadol 25:1; fentanyl 1:100; hydromorphone 1:5; and meperidine 7.5:1 [21-24]. Other secondary outcomes were: nausea; vomiting; pruritus; pre-operative anxiety; confusion; urinary retention; respiratory depression; constipation; dizziness or light-headedness; sedation or drowsiness or somnolence; visual disturbance; headache; and patient satisfaction.

We converted pre-operative anxiety, patient satisfaction and pain scores to a ten-point scale. We analysed postoperative pain scores and 24 h morphine consumption as mean differences and dichotomous outcomes as risk ratios [25]. We estimated from graphs unavailable numerical data. We estimated unavailable standard deviations from other trials in the analysis [26]. We used random-effects models and used the Cochrane tool to assess risks of bias [27]. We assessed statistical heterogeneity with the I^2 statistic and Cochran’s Q, for which we regarded $p < 0.1$ as significant. We used Egger’s regression test to assess funnel plots for small study effects ($p < 0.1$). We considered using Duval and Tweedie’s ‘trim and fill’ analysis and calculating Orwin’s ‘failsafe N’, but decided not to given substantial between-trial heterogeneity [16, 28, 29].

We performed a method of moments meta-regression to assess the impact of morphine consumption or pain score in the control group, gabapentin dose, type of anaesthesia and type of surgery on effect estimates [30]. We selected the model that explained the larger proportion of between study heterogeneity, using hierarchical entry. We assessed heteroscedasticity, linearity and outliers from studentised residual plots and we assessed collinearity using variance inflation factor. We used Cook’s distance to assess the model for influential cases. Results are presented as the total proportion of between study heterogeneity explained by the model (R^2) with a corresponding p value. We constructed a multivariate model in order to produce a predictive formula to determine the efficacy of gabapentin for the primary outcome using the general formula:

$$\text{Reduction in morphine consumption (mg)} = \beta_0 + \beta_1 X_1 + \beta_2 X_2 \dots \beta_i X_i,$$

where β_0 = intercept/constant and $\beta_{1, 2, \dots, i}$ is the first to the i th coefficient of the first to the i th independent variable ‘X’.

We performed sensitivity analyses by removing studies at high risk of bias, removing studies where standard deviations were estimated and by removing studies that gave additional postoperative doses. We used Review Manager 5.3 [31] and Comprehensive Meta-analysis 3 [32].

Results

Figure 1 and Table 1 detail the 133 trials we included in the review, with our categorisation of risks of bias in Figure 2 [33-164]. We excluded one duplicate trial [165], three trials that were unavailable as full text [166-168], five trials that did not use a placebo [169-173], one trial that used combination therapy [174] and two uncontrolled trials [175, 176].

Gabapentin reduced the postoperative dose of opioid given in the first 24 h (Fig. 3), but with substantial 98% statistical heterogeneity, $p < 0.001$. The asymmetric funnel plot (Fig. 4) indicated small study effects, $p < 0.001$. Gabapentin reduced opioid consumption by an amount that correlated with the opioid consumption by the control group, $R^2 81\%$, $p < 0.001$ (Fig. 5). The residual variation in gabapentin effect was largely accounted for by the increasing effect with gabapentin dose and general anaesthesia (compared with subarachnoid anaesthesia), with R^2 increasing to 90%, $p < 0.001$. The type of surgery was not independently associated with gabapentin effect. The results were insensitive to the removal of trials at high risk of bias or those for which standard deviations were estimated or the removal of trials that gave additional postoperative doses.

The reduction in consumption of morphine equivalents (mg) by gabapentin = $3.73 + (-0.378 \times \text{control morphine consumption}) + (-0.0023 \times \text{gabapentin dose}) + (-1.917 \times \text{anaesthetic type})$,

where 'anaesthetic type' takes the value of 1 for general anaesthesia and 0 for subarachnoid anaesthesia.

For example, a gabapentin dose of 1200 mg with general anaesthesia would be expected to reduce a 24 h control morphine consumption of 30 mg by:

$$3.73 + (-0.378 \times 30) + (-0.0023 \times 1200) + (-1.917 \times 1) = 12.29 \text{ mg.}$$

Conversely, a gabapentin dose of 600 mg with subarachnoid anaesthesia would be expected to reduce a 24 h control morphine consumption of 10 mg by:

$$3.73 + (-0.378 \times 10) + (-0.0023 \times 600) + (-1.917 \times 0) = 1.43 \text{ mg.}$$

Gabapentin reduced postoperative pain throughout the first 24 h, with substantial 80% statistical heterogeneity, $p < 0.001$. The mean (95% CI) reduction in pain score (on a ten-point scale) in the first hour was 1.68 (1.35-2.01) points, $p < 0.001$. The mean (95% CI) point reductions at 2 h, 6 h, 12 h and 24 h were: 1.21 (0.88-1.55), $p < 0.001$; 1.28 (0.98-1.57), $p < 0.001$; 1.12 (0.91-1.33), $p < 0.001$; and 0.71 (0.56-0.87), $p < 0.001$. There was evidence of small study effects at: one hour, $p = 0.06$; six hours, $p = 0.004$; 12 h, $p = 0.014$; and at 24 h, $p = 0.05$. The postoperative analgesic effect of gabapentin increased with increasing pain score in the control group and the type of surgery, $R^2 23\%$ - 61% for 1, 12h and 24 h, $p < 0.001$ for all time points. Control pain score and gabapentin dose explained the majority of the heterogeneity between studies at 2 h; $R^2 59\%$, $p < 0.001$. Control group pain score, gabapentin dose and type of surgery explained the majority of the heterogeneity at 6 h; $R^2 65\%$, $p < 0.001$.

Gabapentin reduced the rates of postoperative nausea, vomiting and pruritus but increased sedation (Table 2). Gabapentin reduced chronic pain score in eight trials at three postoperative months by a mean (95% CI) of 0.43 (0.00-0.86) points, $p = 0.05$. Chronic pain was unaffected at other times. No trial reported chronic pain

at 12 months. There was substantial 78% heterogeneity, $p < 0.001$, but without evidence of small study effects ($p = 0.33$).

Gabapentin reduced pre-operative anxiety on a ten-point scale by a mean (95% CI) of 1.52 (0.78-2.26) points in eight trials, but with substantial heterogeneity of 85%, $p < 0.001$ and evidence of small study effects, $p = 0.09$. The reduction in anxiety by gabapentin was correlated with the higher anxiety score in the control group, R^2 86%, which was also correlated with gabapentin dose, R^2 increasing to 91%, $p < 0.001$ for both. Gabapentin improved postoperative patient satisfaction on a ten-point scale by a mean (95% CI) of 0.89 (0.22-1.57) points, $p = 0.01$. However, there was substantial 81% heterogeneity, $p < 0.001$, without evidence of small study effects ($p = 0.30$).

Discussion

We found that peri-operative gabapentin reduced opioid consumption and pain scores during the first 24 h after surgery. Greater opioid consumption and worse pain in the control group were associated with greater gabapentin analgesia. Gabapentin also reduced pre-operative anxiety and postoperative nausea, vomiting and pruritus whilst it increased patient satisfaction and postoperative sedation. Gabapentin reduced chronic pain at three postoperative months, for which there was less evidence than the other effects. Small study effects were evident for many outcomes, raising the possibility of publication bias.

The analgesic effect of gabapentin was determined by the type of surgery only insofar as the amount of pain the surgery caused. Consider four patients having an operation, two spinal and two abdominal, with one patient in each group experiencing severe postoperative pain and requiring a lot of morphine postoperatively and the other patient having little of either. The expected effect of prophylactic gabapentin on opioid consumption would be determined by the patient's pain and not by the type of operation that they had had. Indeed, despite greater reductions in opioid consumption in certain procedures, type of surgery was not in itself independently associated with heterogeneity between studies. This finding is consistent with previous research, which has shown larger absolute reductions in pain with higher pain scores [177].

Previous groups have advocated the use of procedure-specific evidence as a way of limiting heterogeneity between postoperative pain trials, largely based on the observed differences in analgesic efficacy between different procedures [12, 178]. Our results suggest this difference may largely be due to different levels of pain within surgical subtypes rather than type of surgery itself. Indeed, even within surgical subgroups statistical heterogeneity was still substantial, most of which was accounted for by the control group morphine consumption. Such differences in morphine consumption within certain surgical subtypes may be due to different procedures within a trial [142], for instance open versus laparoscopic surgery, different procedures within surgical subgroups (ENT for example), variation in other analgesic drugs and techniques, genetic variations in participants and variations in the prescribing practices of attending doctors and the administration practices of nursing staff. The lack of an association between type of surgery and 24-h opioid consumption is in agreement with a recent meta-analysis of pregabalin [179].

The dose of gabapentin altered the analgesic effect less than the amount of pain. The effect of gabapentin dose was inconsistent for all outcomes, with dose only explaining a small proportion of the variation [179]. Some randomised controlled trials have suggested that the maximum effective analgesic dose of gabapentin is 600 mg or 900 mg, whilst others have suggested a median effective dose of 1500 mg [114, 119, 180]. The postoperative effects of gabapentin appear equivalent when given before or after surgery [42, 93, 114, 164]; it is more convenient for patients to swallow gabapentin than to administer it down a nasogastric tube, whilst some patients might benefit from gabapentin's sedative effects pre-operatively. This suggests future trials should aim to use pre-operative dosages between 600-1200 mg.

The significant small study effects indicate possible publication bias in favour of the analgesic effect of gabapentin, but arguably with a bias at the expense of gabapentin for sedation and dizziness [15]. The conclusions of meta-analyses uninformed by analyses of possible publication bias may overstate the effects of gabapentin [6-11]. Publication bias is one reason why the results of meta-analyses and subsequent large randomised controlled

trials disagree [16]. However, other causes of an asymmetrical funnel plot include larger effects in small studies, sampling variation and possible fraud.

There are several limitations with this review. Firstly, the presence of statistical heterogeneity, indirectness of evidence and possible publication bias reduce the strength of recommendations from the review according to GRADE criteria [17]. Secondly, the use of meta-regression is prone to aggregation bias and confounding inherent in observational studies. For example, gabapentin was less effective after spinal anaesthesia, but the cause might be the type of surgery (orthopaedic, caesarean section and joint arthroplasty) with which spinal anaesthesia was used more often. Thirdly, the risks of bias were unclear for many trials, particularly for allocation concealment, which may distort effect estimates in favour of gabapentin [181].

We would recommend against further small randomised controlled trials. Trials should aim to recruit more participants to investigate dose-responses effects and infrequently reported outcomes, such as chronic pain and postoperative confusion. Trial sample sizes should account for the expected severity of pain in the control group, which will be the main determinant of gabapentin effect and the precision of the results. Future meta-analyses of other postoperative analgesic agents might investigate heterogeneity of results through meta-regression of the covariates used in this review.

In conclusion, peri-operative gabapentin was analgesic, with the absolute effect being proportionate to the postoperative severity of pain and opioid requirement without gabapentin. The effect of gabapentin was not independently associated with the type of surgery. Gabapentin also reduced pre-operative anxiety, postoperative nausea, vomiting and pruritus, and increased patient satisfaction, at the expense of increased sedation. The absolute effects may be overestimated by publication bias.

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Table 1 Characteristics of included studies.