Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery


Department of Anaesthesia and Intensive Care Medicine, Helsinki University Hospital, PO Box 140, Helsinki FI-00029 HUCH, Finland

*Corresponding author. E-mail: ritva.m.jokela@hus.fi

Background. Multimodal pain management has been suggested to improve postoperative analgesia. In this study, we evaluated the quality of analgesia in women undergoing day-case gynaecological laparoscopic surgery, after premedication with pregabalin 75 mg (P75) or 150 mg (P150), compared with diazepam 5 mg (D5). All patients were given ibuprofen 800 mg orally.

Methods. Altogether 90 consenting women were anaesthetized in a standardized fashion. Postoperative analgesia was provided by ibuprofen 800 mg twice a day with fentanyl i.v. on request in the recovery room (RR), and combination tablets with acetaminophen and codeine after the RR. The visual analogue scale (VAS) scores for pain and side-effects and the amounts of postoperative analgesics were recorded for 24 h after surgery. The areas under the curves (AUC) were calculated for the VAS scores for pain at rest, pain in motion, and pain at cough 1–8 and 1–24 h after surgery.

Results. The median AUC values for VAS scores for pain at rest ($P = 0.048$) and in motion ($P = 0.046$) 1–8 h after surgery were lower in the P150 group than that in the D5 group. The amounts of rescue analgesics or the degree of drowsiness did not differ in the three study groups.

Conclusions. Analgesia was better after premedication with pregabalin 150 mg than after diazepam 5 mg, both with ibuprofen 800 mg, during the early recovery after day-case gynaecological laparoscopic surgery. Pregabalin 150 mg did not reduce the amount of postoperative analgesics required.

Br J Anaesth 2008; 100: 834–40

Keywords: pain, postoperative; premedication, diazepam; premedication, pregabalin; surgery, day-case

High-quality pain control after day-case surgery is still a major challenge.1,2 Although opioids continue to have an important role in postoperative pain management, they have side-effects.3 A multimodal approach has been suggested to improve postoperative analgesia and to reduce the opioid-related side-effects.4 Pregabalin and gabapentin, the developmental predecessor of pregabalin, are structural analogues of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA), but they are not functionally related to it.5 In rodent models of chronic neuropathic pain, pregabalin has showed superior analgesic potency compared with gabapentin.6 The pharmacokinetics of pregabalin has proved to be linear with low variability.7 Pregabalin was developed and launched for treating partial epilepsy and neuropathic pain in Europe and the USA in 2004, and for general anxiety disorder in Europe in 2006.

The analgesic effect of gabapentin has been investigated widely in surgical settings during the past few years. The findings of the trials have been summarized in four recent systematic reviews, which demonstrate that gabapentin has an analgesic and opioid-sparing effect in postoperative pain management.8–11 So far, evidence of the analgesic property of pregabalin in postoperative pain is limited to three controlled randomized trials: one on dental pain,12 one in combination with celecoxib in patients undergoing spinal fusion surgery,13 and one in patients undergoing laparoscopic hysterectomy.14

We hypothesized that the management of postoperative pain would be better if patients undergoing day-case gynaecological laparoscopic surgery were given oral premedication with pregabalin 75 or 150 mg, compared with diazepam 5 mg as an active placebo; all were also given ibuprofen 800 mg.
Methods

After the Institutional Ethics Committee and the National Agency of Medicines approved this randomized, double-blinded, active placebo controlled trial, we obtained the written informed consent from 90 women undergoing day-case gynaecological laparoscopic surgery during 12 months starting September 2006. Finnish-speaking patients over 18 yr of age and with a BMI of 18–35 kg m\(^{-2}\) met the inclusion criteria if they were ASA physical status I–II, did not have contraindications to the use of any of the study medications, or previous or current use of gabapentinoids.

The study patients were premedicated orally 1 h before surgery with the study medication: diazepam 5 mg (the D5 group) as an active placebo, pregabalin 75 mg (the P75 group), or pregabalin 150 mg (the P150 group), all in addition to ibuprofen 800 mg. The hospital pharmacy performed the randomization using a computer-generated random number table. They also masked the study medication by packing diazepam and pregabalin into two identical capsules to make the drugs unrecognizable. The study drugs were further packed and sealed in opaque plastic containers labelled with the randomization numbers. Each consenting patient received a consecutive randomization number. The randomization code was not opened until the final interview of the last study patient was conducted.

In the operating theatre, anxiety was evaluated using a 11-point visual analogue scale (VAS), which the patients were trained to use before premedication. An i.v. access was established, and standard monitoring with ECG, pulse oximetry, non-invasive blood pressure (NIBP) and State Entropy (SE\(^{TM}\), Entropy, General Electrics Healthcare, Helsinki, Finland) was started. A remifentanil infusion was initiated with a dose of 0.2 µg kg\(^{-1}\)min\(^{-1}\) and induction of anaesthesia was achieved with propofol 2.0–2.5 mg kg\(^{-1}\). The propofol infusion was initiated with a dose of 0.1 mg kg\(^{-1}\)min\(^{-1}\) and adjusted to keep the SE\(^{TM}\) level between 45 and 55, and the remifentanil infusion was adjusted to keep NIBP at −15 to +15% of the baseline value minus 20 mm Hg. Tracheal intubation was facilitated with rocuronium 0.6 mg kg\(^{-1}\), and the patients’ lungs were mechanically ventilated with a mixture of oxygen and nitrous oxide (0.5:0.5 litre) to keep the end tidal CO\(_2\) at the level of 4.5–5.0 kPa. After intubation, a gastric tube was inserted to deflate the stomach, and the tube was aspirated and removed before extubation. To prevent postoperative nausea and vomiting (PONV), all patients received dexamethasone 5 mg i.v. immediately after the induction of anaesthesia, and droperidol 0.5–0.75 mg i.v. and ondansetron 4 mg i.v. at the end of surgery. After the operation was completed, the remifentanil infusion was discontinued and a 0.075 mg i.v. bolus of fentanyl was given. During the closure of the skin, propofol infusion was stopped and neostigmine 2.5 mg with glycopyrrolate 0.5 mg i.v. was administered to reverse neuromuscular block. The total amounts of remifentanil and propofol infused and the average values of SE\(^{TM}\) during the anaesthesia were recorded.

In the recovery room (RR), the study nurse treated postoperative pain on request with 0.025 mg doses of fentanyl i.v. The patients received ibuprofen 800 mg orally on the evening of the day of surgery and on the next morning. To treat the breakthrough pain, they received on request combination tablets of acetaminophen and codeine orally. If the patients still had an i.v.-line, the rescue anti-emetic medication was droperidol 0.5 mg i.v. or ondansetron 4 mg i.v. After the i.v.-line was removed, the patients received an ondansetron disintegrating tablet to treat a possible episode of PONV. For the postoperative VAS scores for pain at rest, pain in motion, and pain at cough, the areas under the VAS–time curves 1–8 and 1–24 h were calculated using a linear time scale (AUC\(_{\text{VAS}}\)). Besides pain scores, VAS scores for side-effects including PONV, drowsiness, lack of concentration, dizziness, headache, blurred vision, itching, and number of episodes of postoperative vomiting were recorded at 1, 2, 4, 6, 8, 12, and 24 h after surgery. The patients were telephoned 24–30 h after discharge from hospital and interviewed by the study nurse or one of the investigators who was unaware of the patients’ group. A structured questionnaire was used to inquire the patients’ pain scores, total amounts of analgesics used, possible side-effects, and their satisfaction with the anaesthesia experience and pain treatment.

Power analysis

A power analysis was performed using a power of 80% and an \(\alpha\)-value of 0.05. We anticipated that the consumption of fentanyl would be 3 µg kg\(^{-1}\) after premedication with diazepam 5 mg, and 2 µg kg\(^{-1}\) after premedication with pregabalin 150, with an SD of 1 µg kg\(^{-1}\). Based on these assumptions, a sample size of 16 patients per group was required. When we estimated the sample size using these assumptions, a sample size of 28 patients per study group. Using these two calculations, we decided to randomize 30 patients into each group.

Statistical analysis

Patient characteristics data including ASA physical status classification, smoking habits, and history of PONV or motion sickness, characteristics of the surgery, including different types of surgery, and the incidence of side-effects were analysed using a \(\chi^2\)-test. The patient characteristics data including age and BMI and clinical data including duration of anaesthesia and surgery, doses of remifentanil and propofol, average SE\(^{TM}\) value during anaesthesia, the times to the first dose of rescue analgesic, and the amounts
of postoperative analgesics were compared using ANOVA. Kruskal–Wallis test was used to compare the preoperative VAS scores for anxiety, postoperative pain at rest, in motion, and at cough and postoperative drowsiness. The statistical analysis was performed using the Statistical Package for Social Sciences (SPSS\textsuperscript{TM}), Windows versions 13.0.1 and 14.0. (SPSS Inc., Chicago, IL, USA).

Results

The study was carried out in the operating theatre and on the gynaecological ward in a hospital in Helsinki, Finland. A total of 90 patients were randomized in the study. In the final analysis, there were 84 patients in the data for the first 24 h after surgery. Figure 1 illustrates the flow of the patients through the trial, including the reasons for exclusion.

The data on the patient characteristics did not differ among the three study groups; also the distribution of the different laparoscopic procedures was similar in all groups (Table 1). The duration of anaesthesia, surgery, and the amounts of remifentanil and propofol administered in the three study groups was equal. Furthermore, the average SET\textsuperscript{TM} values did not differ between the groups (Table 1).

The three study groups were very similar on the following points: the patients’ score (0–10) for anxiety on arrival in the operating theatre (Table 2); the times to the first rescue fentanyl dose and the doses of fentanyl in the RR; and the number of patients taking acetaminophen with codeine. VAS scores for pain at rest, in motion, and at cough are presented in Figures 2, 3, and 4, respectively. The AUC values for VAS scores for pain at rest 1–8 h after surgery ($P=0.048$) and in motion ($P=0.046$) were lower in the P150 group than in the D5 group (Table 3). The AUC values for VAS scores for pain at cough did not differ between the three study groups (Table 3). The degree of drowsiness (Fig. 5) and the incidence of side-effects did not differ in the three groups (Table 4). The patients’ satisfaction with anaesthesia and pain management was equal in these study groups (Table 2).

Discussion

In the present study, the VAS scores for pain at rest and in motion were lower during the early recovery after premedication with pregabalin 150 mg than with diazepam 5 mg, all combined with ibuprofen 800 mg. During the later course of recovery, there was no difference in the VAS scores for pain between the groups. This finding is in accordance with the pharmacokinetic profile of pregabalin, which has an elimination half-life of 4.6–6.8 h after a single dose.\textsuperscript{7} However, there was no difference between the groups in the consumption of analgesics after operation. We found a distinct opioid-sparing effect with pregabalin in our previous study, in which the maximum recommended daily dose of pregabalin 600 mg (300 mg as premedication, the dose repeated after 12 h) reduced the amount of postoperative oxycodone, but not the VAS scores for pain.\textsuperscript{14} The difference in the results of these two trials is possibly because of the postoperative rescue analgesic technique. It is easier to demonstrate the difference in the consumption of analgesics with the patient-controlled analgesia system used in our previous study.\textsuperscript{14} All in all, the reduction in the VAS scores for pain shown in the present study indicates a better quality of analgesia.

It is possible that without the multimodal analgesic approach, the analgesic effect of pregabalin would have been clearer in the present study. Apart from the consumption ibuprofen 800 mg given twice a day, the patients received dexamethasone for anti-emetic prophylaxis at the induction of anaesthesia. There is strong evidence that glucocorticoids, besides their anti-emetic activity, have analgesic potency.\textsuperscript{15} The present study was designed to reflect the actual clinical situation. Non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen are the basis of modern pain management after ambulatory surgery, combined with opioids whenever required.\textsuperscript{16}

The goal of multimodal analgesia is not only the improved quality of analgesia, but also the reduction in opioid-related side-effects.\textsuperscript{4} After using multimodal analgesia in the present study, however, we did not find any opioid-sparing impact or reduction in opioid-related side-effects. On the other hand, pregabalin did not increase the incidence of side-effects, either. It is possible that a bigger dose of pregabalin could have more analgesic potency but also more side-effects. In our previous study, we showed a notable opioid-sparing effect with pregabalin 600 mg a day without any concomitant NSAIDs, but we also noted that the incidence of dizziness and blurred vision was higher after the high dose of pregabalin than the 10 mg dose of diazepam.\textsuperscript{14} In the first published clinical trial on pregabalin, in which 50 and 300 mg doses of pregabalin were compared with ibuprofen 400 mg in a dental pain model, the 300 mg dose of pregabalin induced considerably more side-effects than did ibuprofen. The most common of these side-effects were dizziness, somnolence, and vomiting.\textsuperscript{12} In another study, in which a 150 mg dose of pregabalin was compared in combination with celecoxib with both of the analgesics alone after spinal fusion surgery, the incidence of side-effects after the combination of pregabalin 150 mg and celecoxib 400 mg was lower than after placebo.\textsuperscript{13} Judging from the results of all these pregabalin trials, it is possible that the concomitant administration of NSAIDs and pregabalin is beneficial as regards the side-effect profile of pregabalin. In fact, this finding is in accordance with the original idea of a multimodal analgesic approach.\textsuperscript{4}

Pregabalin probably shares the same mechanism of action with gabapentin.\textsuperscript{5} They both bind to the $\alpha$-2-δ subunit of voltage-gated calcium channels,\textsuperscript{17} reducing the release of several excitatory neurotransmitters, including
glutamate, noradrenalin, and substance P. Compared with gabapentin, pregabalin has a predictable and linear pharmacokinetic profile with a time to peak plasma concentration of up to 1 h, and oral bioavailability of ~90%. Pregabalin is only slightly metabolized by the liver and has no activity at P450 enzymes, which results in a lack of pharmacokinetic interaction. Up to 98% of the administered dose of pregabalin is eliminated unchanged by the kidneys.

The highest recommended daily dose of pregabalin is 600 mg, dosed twice a day, and that of gabapentin is 3600 mg, dosed three times a day. The most common dose of gabapentin is 1200 mg in the trials performed on postoperative pain, and this dose has been found to be effective in three systematic reviews published during the past 2 yr. In the present study, the 150 mg dose of pregabalin improved the quality of postoperative analgesia without an opioid-sparing effect. According to the results of the rodent model of chronic neuropathic pain, the analgesic potency of pregabalin is two- to four-fold greater than that of gabapentin. In the literature, however, there are no comparative studies on the analgesic potency of these two gabapentinoids in humans.

Gabapentinoids are regarded as relatively expensive medicines, but the cost of a single premedication dose is low (about £1 for both pregabalin 150 mg and gabapentin 1200 mg). In all, costs of drugs used for anaesthesia constitute only a small fraction of total cost of the procedure.
Fig 2 VAS pain at rest (median, 95% CI) after premedication with diazepam 5 mg, pregabalin 75 mg, and pregabalin 150 mg during 1–24 h after surgery.

Fig 3 VAS pain in motion (median, 95% CI) after premedication with diazepam 5 mg, pregabalin 75 mg, and pregabalin 150 mg during 1–24 h after surgery.
We regard achievement of better pain relief and quicker mobilization with a single dose pregabalin cost-effective.

We chose to use diazepam 5 mg as an active placebo in the control group, as we wanted to compare pregabalin with our routine premedication. Apart from its analgesic potency, pregabalin has anxiolytic properties. In the present study, the level of anxiety was similar after premedication with diazepam 5 mg, pregabalin 75 mg, or pregabalin 150 mg.

The inclusion criteria of the present study were rather strict, which may cause a source of bias. However, pregabalin has been introduced for clinical use only recently. When conducting studies with a newly developed drug, it is not appropriate to include patients with particular risks.

In conclusion, analgesia was better after premedication with pregabalin 150 mg than after diazepam 5 mg, both with ibuprofen 800 mg, during the early recovery after day-case gynaecological laparoscopic surgery. Pregabalin 150 or 75 mg did not reduce the amount of postoperative analgesics required, nor the incidence of side-effects.

**Table 3** VAS pain measurements at rest, in motion, and at cough. Values are median [range]. VAS, visual analogue scale; AUC$_{VAS}$, area under VAS–time curve. For explanations, see Table 1

<table>
<thead>
<tr>
<th></th>
<th>D5 ($n=28$)</th>
<th>P75 ($n=30$)</th>
<th>P150 ($n=26$)</th>
<th>P-value</th>
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<tr>
<td>VAS pain at rest</td>
<td></td>
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<td></td>
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<tr>
<td>AUC$_{VAS}$ 1–8 h</td>
<td>20.00 [1.00, 55.50]</td>
<td>16.50 [8.00, 36.00]</td>
<td>12.00 [2.00, 43.00]</td>
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<td>AUC$_{VAS}$ 1–24 h</td>
<td>38.00 [10.50, 171.50]</td>
<td>41.50 [10.50, 80.00]</td>
<td>36.00 [2.00, 135.00]</td>
<td>0.333</td>
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<tr>
<td>VAS pain in motion</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC$_{VAS}$ 1–8 h</td>
<td>22.50 [4.50, 57.00]</td>
<td>19.25 [4.50, 41.50]</td>
<td>15.75 [2.50, 51.50]</td>
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<td>AUC$_{VAS}$ 1–24 h</td>
<td>47.25 [4.50, 175.00]</td>
<td>55.75 [6.00, 107.00]</td>
<td>40.50 [4.50, 128.50]</td>
<td>0.343</td>
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<tr>
<td>VAS pain at cough</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>AUC$_{VAS}$ 1–8 h</td>
<td>25.00 [6.00, 62.00]</td>
<td>24.75 [11.50, 57.50]</td>
<td>20.00 [1.50, 57.00]</td>
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<td>AUC$_{VAS}$ 1–24 h</td>
<td>65.50 [24.00, 210.00]</td>
<td>64.25 [20.00, 148.50]</td>
<td>52.50 [2.00, 158.00]</td>
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**Table 4** The incidence of side-effects in the three study groups. Values are $n$ (%). POV, postoperative vomiting. For explanations, see Table 1

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<th>D5 ($n=28$)</th>
<th>P75 ($n=30$)</th>
<th>P150 ($n=26$)</th>
<th>P-value</th>
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<tr>
<td>PONV 0–2 h</td>
<td>0</td>
<td>1 (3%)</td>
<td>2 (8%)</td>
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<tr>
<td>PONV 2–24 h</td>
<td>9 (32%)</td>
<td>9 (30%)</td>
<td>12 (46%)</td>
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<tr>
<td>POV 0–2 h</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0.749</td>
</tr>
<tr>
<td>POV 2–24 h</td>
<td>2 (7%)</td>
<td>1 (3%)</td>
<td>2 (8%)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>18 (64%)</td>
<td>16 (53%)</td>
<td>21 (80%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (32%)</td>
<td>8 (27%)</td>
<td>5 (19%)</td>
<td>0.558</td>
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<tr>
<td>Blurred vision</td>
<td>3 (11%)</td>
<td>6 (20%)</td>
<td>7 (27%)</td>
<td>0.313</td>
</tr>
<tr>
<td>Lack of concentration</td>
<td>20 (74%)</td>
<td>20 (67%)</td>
<td>22 (85%)</td>
<td>0.295</td>
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<tr>
<td>Pruritus</td>
<td>2 (7%)</td>
<td>7 (23%)</td>
<td>5 (19%)</td>
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**Fig 4** VAS pain at cough (median, 95% CI) after premedication with diazepam 5 mg, pregabalin 75 mg, and pregabalin 150 mg during 1–24 h after surgery.

**Fig 5** VAS drowsiness (median, 95% CI) after premedication with diazepam 5 mg, pregabalin 75 mg, and pregabalin 150 mg during 1–24 h after surgery.
Acknowledgements
We wish to thank Ms Maria Jokilehto, RN, Ms Eija Ruoppa, RN, and the entire staff of the operation theatre and gynaecological ward in Women’s Hospital, Helsinki University Hospital for taking excellent care of our patients.

Funding
The study was financially supported by the HUCH-EVO Committee, Helsinki, Finland (TYH 5229) and by a grant from the Paulo Foundation, Helsinki, Finland.

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