A placebo-controlled randomized clinical trial of perioperative administration of gabapentin, rofecoxib and their combination for spontaneous and movement-evoked pain after abdominal hysterectomy

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Abstract

Current treatments for post-injury movement-evoked pain are inadequate. Non-opioids may complement opioids, which preferentially reduce spontaneous pain, but may have incomplete efficacy as single agents. This trial evaluates efficacy of a gabapentin–rofecoxib combination following hysterectomy. In addition to IV-PCA morphine, 110 patients received either placebo, gabapentin (1800 mg/day), rofecoxib (50 mg/day) or a gabapentin–rofecoxib combination (1800/50 mg/day) starting 1 h pre-operatively for 72 h. Outcomes included pain at rest, evoked by sitting, peak expiration and cough, morphine consumption and peak expiratory flow (PEF). For placebo, gabapentin, rofecoxib and combination, 24 h pain (100 mm VAS) was: at rest—23.6 ($P<0.05$ vs. all treatments), 13.8, 14.4 and 12.1; during cough—50.7 ($P<0.05$ vs. all treatments), 41.5, 44.8 and 30.8; 48 h morphine consumption (mg) was: 130.4 ($P<0.05$ vs. all treatments), 81.7, 75.6 and 57.2 ($P<0.05$ vs. gabapentin and rofecoxib) and 48 h PEF (% baseline) was 63.9 ($P<0.05$ vs. all treatments), 77.2, 76.7 and 87.5 ($P<0.05$ vs. gabapentin and rofecoxib). Adverse effects were similar in all groups except sedation which was more frequent with gabapentin. Combination and rofecoxib reduced pain interference with movement, mood and sleep ($P<0.05$) and combination was superior to gabapentin for all these three ($P<0.05$). These data suggest that a gabapentin–rofecoxib combination is superior to either single agent for postoperative pain. Other benefits include opioid sparing, reduced interference with movement, mood and sleep and increased PEF suggesting accelerated pulmonary recovery. Future research should identify optimal dose-ratios for this and other analgesic combinations.

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Keywords: Gabapentin; Rofecoxib; Postoperative pain; Movement-evoked pain; Hysterectomy

1. Introduction

While its primary goal is to improve health-related quality of life after surgery, clinical trials data suggest that superior postoperative analgesia, particularly with epidural local anesthetics and/or opioids, may also reduce the risk of postoperative pulmonary dysfunction and complications such as atelectasis and pulmonary infection (Ballanyne et al., 1998). Given the pathogenic contributions of pain-related splinting and hypoventilation to these postoperative complications (Joris et al., 1998; Vassilakopoulos et al., 2000), such benefits are thought to be partly due to the superior relief of movement-evoked pain that has been observed with epidural analgesia (Block et al., 2003). Despite such benefits, regional analgesic techniques are not

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without complications of their own (e.g. hypotension, sensorimotor blockade) which necessitate resource intensive follow-up by in-hospital acute pain services (Block et al., 2003). Although opioids are the mainstay of systemic treatment for moderate to severe postoperative pain (McQuay et al., 1999; Walder et al., 2001), postoperative studies have shown that doses of opioids producing complete relief of spontaneous pain have relatively little effect on movement-evoked pain (Tverskoy et al., 1996; Wilder-Smith et al., 1999). Systemic NSAIDs can be used to complement opioids for postoperative movement-evoked pain, however, they are limited by well-known gastrointestinal, renal and hematological toxicities and, thus, the search for alternative therapies continues.

Since almost any single, maximally dosed, drug has incomplete efficacy and predictable toxicities, combining different analgesic drugs may provide additional benefits following surgery. Rofecoxib and gabapentin are two well-tolerated and mechanistically diverse drugs that have each shown promise in the management of postoperative pain. Rofecoxib is one of several selective inhibitors of the cyclooxygenase-2 enzyme (Chan et al., 1999) which has been shown to reduce inflammatory pain with less gastrointestinal toxicity than traditional NSAIDs (Bombardier et al., 2000). Several clinical trials have evaluated the safety and efficacy of rofecoxib in the management of postoperative pain (Barden et al., 2002) and examples of observed benefits include partial reduction of spontaneous (Morrison et al., 1999) and movement-evoked (Reuben et al., 2002) pain, opioid sparing (Reuben and Connelly, 2000) and, in some situations, accelerated physiological recovery following surgery (Sinatra et al., 2004). Gabapentin is a 3-alkylated analog of gamma-amino butyric acid (GABA) whose foremost putative mechanism is the modulation of alpha-2-delta calcium channel subunits (Gee et al., 1996). Several recent trials have evaluated the safety and efficacy of gabapentin in postsurgical pain and observed benefits also include partial reduction of spontaneous (Fassoulaki et al., 2002) and movement-evoked (Dirks et al., 2002) pain as well as opioid sparing (Dierking et al., 2004). Previous laboratory studies suggest that gabapentin interacts synergistically with naproxen (Hurley et al., 2002). Thus, rofecoxib and gabapentin appear to have distinct analgesic mechanisms which may interact favorably in combination.

Thus, the purpose of this trial is to evaluate the safety and analgesic efficacy of a rofecoxib–gabapentin combination in comparison with either single agent following surgery. While clinical trial designs are commonly restricted to a single primary outcome measure, the use of multiple trial outcomes, in certain situations, has been recently advocated in order to maximize the information gathered about a particular intervention (Berger, 2002). Given previous evidence that gabapentin and rofecoxib reduce both spontaneous and evoked pain, this trial was designed to comprehensively detect these diverse effects for a combination of gabapentin and rofecoxib.

2. Methods

2.1. Participants

This trial received institutional ethics approval. All patients were enrolled between August 2001 and October 2003 following informed consent. Eligible patients fit an ASA I or II classification prior to abdominal hysterectomy through a low transverse incision. Trial exclusions were: (1) hypersensitivity to any study drugs, (2) serious organ disease/dysfunction, (3) persistent preoperative pain, (4) daily intake, or intake 48 h preoperatively, of any analgesic, (5) alcohol/substance abuse, (6) a major psychiatric disorder, (7) a bleeding disorder, (8) peptic ulcer disease, (9) asthma/COPD and (10) a seizure disorder.

2.2. Study design

This was a single center, parallel randomized trial with four treatment groups: (a) gabapentin 1800 mg/day, (b) rofecoxib 50 mg/day, (c) a combination of gabapentin 1800 mg/day and rofecoxib 50 mg/day (combination), or (d) placebo. Study medications were encapsulated in red and gray gelatin capsules, respectively, by the Kingston General Hospital Investigational Pharmacy (KGH-IP) in order to maintain double-blind conditions. At study commencement, a pharmacist from the KGH-IP prepared a concealed treatment allocation schedule which randomized these four treatments, in blocks of four, to a series of patient numbers. Following informed consent, enrolled patients were assigned the next consecutive patient number and the corresponding set of study medications were dispensed by the KGH-IP. Nursing staff administered and observed study medication consumption. The selected dose of 50 mg/day for rofecoxib was based on experience published at the time of study conception (Morrison et al., 1999). Although gabapentin doses of 3600 mg/day can be reached through slow titration over a period of weeks in the setting of chronic pain (Rowbotham et al., 1998), we selected a considerably lower gabapentin dose (1800 mg/day) for this trial since study patients were gabapentin-naive and there would be no opportunity for gradual dose-titration. Patients received red capsules and gray capsules which were identical in appearance across treatment groups as per a double dummy design. Two red capsules (each containing either rofecoxib 25 mg or placebo) were administered once daily in the morning starting preoperatively on the day of surgery (1 h pre-op) and continuing through postoperative days 1 and 2. Two gray capsules (each containing either gabapentin 300 mg or placebo) were administered three times daily starting preoperatively on the day of surgery (1 h pre-op) and continuing through postoperative days 1 and 2 (the midday dose of gray capsules was omitted on the day of surgery).

2.3. Protocol

Intraoperatively, patients received a balanced anesthetic at the discretion of the attending anesthesiologist who was blinded to treatment. Intravenous fentanyl (3–5 mcg/kg), was administered within the first 30 min of surgery. Intravenous morphine
(0.1–0.2 mg/kg) was administered over 30 min, starting 30 min before anticipated completion of surgery. No local or regional anesthesia or any other analgesic drugs were used perioperatively. All patients received ondansetron 4 mg IV, 30 min before anticipated completion of surgery. Following surgery, all patients received patient-controlled analgesia (PCA) with intravenous morphine as the only non-study drug analgesic and were followed on a daily basis by a study nurse and the staff of the acute pain service (APS). In the postanesthetic care unit (PACU), nurse-delivered morphine boluses were administered until patients were alert enough to use a PCA pump. PCA was set to deliver 1.0 mg with a lock-out of 6 min, and no continuous infusion. If necessary at any time during the study, this could be increased up to 2.0 mg and the lock-out time shortened down to 5 min. PCA was discontinued at the discretion of the APS upon diminishing frequency of use and patients could subsequently receive oral morphine 5–10 mg every 3 h as needed as the only non-study analgesic. Ondansetron 4 mg IV was continued every 8 h for the first 36 h postoperatively and dimenhydrinate 25 to 50 mg IV every 4 h was allowed, as needed. Headache unresponsive to study medications or PCA morphine could be treated with acetaminophen (for headache only) 650 mg every 4 h as needed. If, at any time during the trial, patients complained of intolerable pain, this would be discussed between the patient, the principal investigator and the APS. Study withdrawal and alternative open-label pain treatments would then be offered as per the acute pain service but treatment code would not be broken. On the hospital ward, patients were encouraged to use an incentive spirometer 5–10 times an hour, and given an abdominal splinting pillow to facilitate coughing. A respiratory therapist evaluated each patient every 8 h and instituted oxygen therapy for an oxygen saturation of less than 92%.

2.4. Outcomes

The primary outcome was pain intensity, at rest and with movement, during the first and second postoperative days. During postanesthetic recovery on the day of surgery, rest pain only was rated verbally (0–10 numerical rating scale) and included as a secondary outcome. Other secondary outcome measures included pain intensity 30 days postoperatively as well as morphine consumption, total time receiving PCA, an integrated analgesic assessment score (Silverman et al., 1993), peak expiratory flow (PEF), pain-related interference, patient satisfaction with pain control, frequency of adverse effects, oxygen saturation, supplemental oxygen requirements, acetaminophen consumption for headache, a blinding questionnaire and time to hospital discharge.

Baseline PEF was measured preoperatively. On the day of surgery, pain (0–10 numerical rating scale), side effects (0, none; 1, mild; 2, moderate; 3, severe), morphine consumption (mg), oxygen saturation (%) and supplemental oxygen requirements were recorded hourly by a study nurse after surgery. At each designated time point on postoperative days 1 and 2, pain (0, 100 visual analog scale [VAS]) was measured as per the following progression: (1) pain at rest, (2) pain evoked by sitting, in a standardized fashion, from the supine position, followed by a 120 s rest period, (3) pain evoked by peak expiration using a peak flow meter (Vitalograph®, Ennis, Ireland) followed by a 120 s rest period, and finally (4) pain evoked by cough. The measurement of PEF and pain evoked by peak expiration involved three forced expirations and only the highest VAS score and PEF (l/min) were recorded. Thus, the obtained expiration-evoked pain measure at each time point may have been from any of the three performed peak expirations. Pain, side effects, morphine consumption, oxygen saturation, supplemental oxygen requirements and acetaminophen consumption were recorded starting at 8 AM and then every four hours until 8 PM for the first two postoperative days. Cumulative morphine consumption included IV morphine administered by nurses in the PACU. For the calculation of cumulative morphine consumption subsequent to discontinuation of IV PCA morphine, oral morphine doses were converted to intravenous doses using a 3:1 ratio (Myoshi and Leckband, 2001). Pain interference, patient satisfaction and blinding questionnaires were completed on the afternoon of postoperative day 2. Time of arrival in the PACU and time of discharge from hospital were recorded. Patients were contacted by telephone on postoperative day 30 in order to rate their pain (0 10 NRS): (1) at time of telephone interview, (2) worst pain in the past week, (3) when sitting up from lying, and (4) while coughing.

2.5. Statistics

Sample size calculation was based on the null hypothesis of no pain difference across all groups. Based on previous (Dahl et al., 2000) variance estimates (SD = 15–23 mm [100 mm VAS]) and after adjusting for five pairwise comparisons (placebo vs. each active drug plus combination vs. each single agent), we calculated that a sample of 25 patients per group would detect, with 80% power, a mean pain difference of 10 mm between any two groups at an overall alpha level of 0.05. Accounting for previously observed dropout rates of approximately 10%, we anticipated the enrollment of 28 patients to yield approximately 25 complete patients per group. Repeated continuous measures, such as pain, morphine consumption and PEF were analyzed by the following method: A linear mixed model with terms of treatment and interaction between treatment and time were first fitted with the data (Verbeke and Molenberghs, 1997). If the interaction term was significant, the treatment groups were then compared at each time point by testing appropriately formed contrasts of the model parameters. Otherwise, a model with treatment variable only was refitted. Continuous data measured at one single point, such as pain on day 30, pain interference and patient satisfaction, or obtained as a summary measure for repeated measures such as time to hospital discharge and lowest oxygen saturation, were analyzed using the method of nonparametric analysis of variance with the Wilcoxon test as a special case when there are two groups (Lehmann, 1975). Proportion data such as frequency of adverse effects and patients requiring oxygen or acetaminophen were analyzed using Fisher’s exact method (Agresti, 1990). For all analyses, the five pairwise comparisons at 0.05 level were only made if the overall test for the difference among all groups was significant at the 0.05 level. This Fisher’s least significant difference (LSD) method, provides protection for multiple comparisons (Snedecor and Cochran, 1980). As initially described by Silverman et al. (1993), a composite measure of pain intensity and morphine consumption was calculated. Pain scores and morphine consumption for each patient were rank ordered, subtracted from the mean rank, expressed as a percentage difference from the mean rank and added together (i.e. pain rank score + morphine rank score) to yield and integrated analgesic assessment score (anywhere from −200 to +200% with the greatest positive score indicating the most
The resulting integrated analgesic assessment scores were analyzed with the Kruskal Wallis test and, when indicated, non-parametric Student–Newman–Keuls post-hoc procedure (Hirsch and Riegelman, 1992). All statistical analyses were conducted using SAS (statistical analysis system) software version 7.

3. Results

3.1. Subjects

Fig. 1 describes patient flow through the trial which was conducted between August 2001 and October 2003.

Regardless of the timing of trial exit, all patients receiving study drug were tracked for major adverse reactions. Due to unexpected operating room closures, surgery was cancelled after study drug administration to two patients. Three patients were withdrawn from the trial within the first hour after surgery and excluded from the efficacy analysis because of the need for administration of non-study analgesics: One developed a new urticarial rash minutes after intraoperative morphine administration, one inadvertently received a non-study NSAID in the operating room and one was offered a nerve block due to intolerable pain within the first hour postoperatively. Two patients underwent repeat laparotomy within the first two postoperative...
days (1, peritonitis due to inadvertent bowel injury; 1, intraabdominal hematoma) and were excluded from the efficacy analysis because of the inability to distinguish posthysterectomy pain from that of the intraabdominal complication. Eight patients were withdrawn during the first two postoperative days due to inadequate analgesia or adverse reactions, however, outcomes from these patients up until withdrawal were included for analysis (Fig. 1). Table 1 describes the demographic and baseline characteristics of patients included in the efficacy analysis. No significant differences were observed across the four treatment groups.

3.2. Outcomes

3.2.1. Pain intensity

Fig. 2 shows mean spontaneous and evoked pain scores. To summarize these data, the analgesic efficacy of combination treatment was superior to placebo for all pain

![Image of Table 1](https://via.placeholder.com/150)

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Age (years)</th>
<th>Race, No. (%)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>Peak expiratory flow (l/min)</th>
<th>Pre-menopausal, No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=24)</td>
<td>42.5 (6.8)</td>
<td>Caucasian, 23 (96)</td>
<td>73.1 (12.6)</td>
<td>1.62 (0.07)</td>
<td>344.8 (42.2)</td>
<td>22 (92)</td>
</tr>
<tr>
<td>Gabapentin (n=23)</td>
<td>43.7 (8.8)</td>
<td>Caucasian, 22 (96)</td>
<td>76.3 (12.1)</td>
<td>1.67 (0.07)</td>
<td>339.5 (48.2)</td>
<td>20 (87)</td>
</tr>
<tr>
<td>Rofecoxib (n=29)</td>
<td>46.3 (9.2)</td>
<td>Caucasian, 28 (97)</td>
<td>74.0 (14.0)</td>
<td>1.64 (0.08)</td>
<td>335.3 (56.7)</td>
<td>25 (86)</td>
</tr>
<tr>
<td>Combination (n=27)</td>
<td>45.1 (8.4)</td>
<td>Caucasian, 27 (100)</td>
<td>75.8 (13.2)</td>
<td>1.64 (0.06)</td>
<td>348.5 (58.6)</td>
<td>23 (85)</td>
</tr>
</tbody>
</table>

Values in parentheses corresponding to age, weight, height and peak expiratory flow indicate SD.
measures throughout postoperative days 1 and 2 and also superior to gabapentin treatment during most of these time points for pain evoked by sitting. Gabapentin was superior to placebo for most of postoperative day 1 for all measures except pain evoked by sitting. Rofecoxib was superior to placebo for almost all time points for pain at rest, evoked by sitting, and evoked by peak expiration, but only on postoperative day 2 for pain evoked by cough. Following anesthetic recovery on the day of surgery, mean pain scores were lower than in the placebo group for gabapentin during the first 4 h postoperatively, and for combination at 3 and 4 h postoperatively; mean pain scores were lower than the combination group for the gabapentin group at 1 and 2 h.

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Postoperative pain at rest (0–10 numerical rating scale)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>6.5 (0.4)</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>4.3 (0.4)</td>
</tr>
<tr>
<td>Rofecoxib</td>
<td>6.4 (0.3)</td>
</tr>
<tr>
<td>Combination</td>
<td>6.1 (0.5) b</td>
</tr>
</tbody>
</table>

Data are presented as mean (SEM). Analysis revealed a significant treatment by time interaction \((P < 0.001)\). *Placebo different only from gabapentin \((P < 0.001)\), †placebo different only from gabapentin \((P = 0.0013–0.029)\) and combination \((P = 0.016–0.021)\), ‡gabapentin different from combination \((P = 0.0035–0.04)\).

![Cumulative morphine consumption](image.png)

![Interval morphine consumption](image.png)

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Fig. 3. Morphine consumption. (A) Cumulative morphine consumption: Analysis revealed a significant treatment by time interaction \((P < 0.001)\). †Placebo different from gabapentin and combination \((P = 0.006–0.042)\). ‡Combination different from rofecoxib \((PP = 0.001–0.049)\). *Placebo different from gabapentin \((P = 0.006–0.042)\). + Placebo different from combination \((P = 0.001–0.015)\). ‡Combination different from rofecoxib \((P = 0.028–0.049)\).

(B) Interval morphine consumption: △ Different from combination \((P = 0.023–0.046)\). †Different from placebo \((P = 0.0001–0.031)\).
after surgery (Table 2). No significant differences in pain scores were observed at telephone follow-up 30 days after surgery (data not shown).

3.2.2. Morphine consumption, integrated analgesic assessment and peak expiratory flow

During postanaesthetic recovery, cumulative morphine consumption was lower than in the placebo group for both gabapentin and combination on postoperative hours 2–8, and lower than in the rofecoxib group for combination on postoperative hours 2–4 (Fig. 3A). Throughout postoperative days 1 and 2, mean cumulative morphine consumption with combination was significantly lower than placebo, lower than gabapentin on the last time point of postoperative day 1 and lower than both gabapentin and rofecoxib throughout all of postoperative day 2. Also, morphine consumption with gabapentin and rofecoxib was lower than placebo on the last timepoint of postoperative day 1 and all of postoperative day 2 (Fig. 3A). Interval morphine consumption during combination treatment was significantly lower than rofecoxib at 0–2 h and significantly lower than gabapentin at 4–8, 20–32 and 32–44 h intervals (Fig. 3B). Twenty-four hours after surgery, percentages of patients still receiving PCA were: placebo, 96%; gabapentin, 91%; rofecoxib, 90% and combination, 52% (P < 0.05 compared to all other groups). Forty-eight hours after surgery, percentages of patients still receiving PCA were: placebo, 27%; gabapentin, 10%; rofecoxib, 12% and combination, 7% (no significant differences). Analysis of integrated analgesic assessment scores demonstrated greater separation between combination and single-agent therapy (Fig. 4). At 24 h after surgery, integrated analgesic assessment scores during combination treatment were significantly lower than gabapentin (but not rofecoxib) for pain evoked by sitting, peak expiration and cough. At 48 h after surgery, integrated analgesic assessment scores during combination treatment were significantly lower than gabapentin (but not rofecoxib) for pain at rest, peak expiration and cough. At 48 h after surgery, integrated analgesic assessment scores during combination treatment were significantly lower than gabapentin (but not rofecoxib) for pain at rest and peak evoked by peak expiration (Fig. 4). PEF (Fig. 5) was higher than placebo for all active treatments throughout postoperative days 1 and 2. Mean PEF with combination was significantly higher than both gabapentin and rofecoxib throughout postoperative days 1 and 2 (Fig. 5).

3.2.3. Adverse effects, pain-related interference and blinding questionnaires

No major adverse events were encountered during the trial follow-up period other than those described in the Subjects paragraph above. Table 3 describes the frequency of treatment-emergent, moderate or severe adverse effects as well as pain-related interference.

Fig. 4. Integrated analgesic assessment. Data are presented as box plots with estimates of the median (centre line), quartile range (box) and 1.5 times the interquartile range (whiskers). P, placebo; G, gabapentin; R, rofecoxib; C, combination. *Different from placebo (P < 0.05). †Different from combination (P < 0.05).

Fig. 5. Peak expiratory flow. Analysis revealed a significant treatment by time interaction (P < 0.001). *Placebo different from gabapentin (P = 0.002–0.0032), rofecoxib (P = 0.0001–0.02) and combination (P < 0.001 throughout). †Combination different from gabapentin (P = 0.0007–0.046) and rofecoxib (P = 0.0025–0.006).
Table 3  
Treatment-emergent adverse effects and pain-related interference

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Adverse effects (No. patients (%))</th>
<th>Pain-related interference [0–10 (SEM)]</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No side effect whatsoever</td>
<td>Dry mouth</td>
</tr>
<tr>
<td>Placebo (n=24)</td>
<td>1 (4.2)*</td>
<td>9 (37.5)</td>
</tr>
<tr>
<td>Gabapentin (n=23)</td>
<td>1 (4.3)</td>
<td>12 (52.2)</td>
</tr>
<tr>
<td>Rofecoxib (n=29)</td>
<td>7 (24.0)</td>
<td>13 (44.8)</td>
</tr>
<tr>
<td>Combination (n=27)</td>
<td>7 (25.9)</td>
<td>12 (44.4)</td>
</tr>
</tbody>
</table>

Adverse effects: *Different from combination (P=0.04), † different from placebo (P=0.045), ‡ different from placebo (P=0.006) and combination (P=0.048). Interference with movement: ††placebo different from rofecoxib (P<0.001) and combination (P<0.001), †‡combination different from gabapentin (P=0.02). Interference with mood: †††placebo different from rofecoxib (P<0.001) and combination (P<0.001), ††‡combination different from gabapentin (P=0.01). Interference with sleep: ††††placebo different from rofecoxib (P=0.002) and combination (P<0.001), †††‡combination different from gabapentin (P=0.02).

Table 4  
Patient and study nurse blinding questionnaire responses

<table>
<thead>
<tr>
<th>Patient</th>
<th>Correct predictions [No. (%)] (i.e. placebo vs. active drug)</th>
<th>Basis for correct predictions (i.e. presence or absence of)</th>
<th>Random probability (% of guessing treatment correctly)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[No. (%)]</td>
<td>Pain relief</td>
<td>Side effects</td>
</tr>
<tr>
<td>Placebo (n=21 completed questionnaires)</td>
<td>9 (42.9)</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Gabapentin (n=21 completed questionnaires)</td>
<td>14 (66.7)</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>Rofecoxib (n=26 completed questionnaires)</td>
<td>20 (76.9)</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Combination (n=24 completed questionnaires)</td>
<td>23 (95.8)</td>
<td>0</td>
<td>18</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study nurse</th>
<th>Correct predictions [No. (%)] (i.e. placebo vs. active drug)</th>
<th>Basis for correct predictions (i.e. presence or absence of)</th>
<th>Random probability (% of guessing treatment correctly)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[No. (%)]</td>
<td>Pain relief</td>
<td>Side effects</td>
</tr>
<tr>
<td>Placebo (n=21 completed questionnaires)</td>
<td>7 (33.3)</td>
<td>0</td>
<td>7</td>
</tr>
<tr>
<td>Gabapentin (n=21 completed questionnaires)</td>
<td>16 (76.2)</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Rofecoxib (n=26 completed questionnaires)</td>
<td>22 (84.6)</td>
<td>0</td>
<td>20</td>
</tr>
<tr>
<td>Combination (n=24 completed questionnaires)</td>
<td>23 (95.8)</td>
<td>0</td>
<td>22</td>
</tr>
</tbody>
</table>

Compared to placebo, significantly more patients reported no side effect whatsoever with combination. Adverse effects were roughly similar in all groups except sedation which was more frequent with gabapentin. Pain interference with movement, mood and sleep was lower than placebo for both rofecoxib and combination and lower than gabapentin for combination only (Table 3). No significant differences were observed across treatment groups with respect to acetaminophen consumption, O₂ requirements/saturation, discharge time, pain-related interference patient satisfaction (data not shown). Table 4 describes patient and study nurse blinding questionnaire responses. There was a trend for patients receiving placebo or combination to correctly predict their treatment slightly more than expected due to chance. However, correct placebo predictions by patients were reportedly equally based on pain relief and side effects. Correct combination predictions were reportedly based mostly on the presence or absence of side effects. Also, there was a trend for the study nurse to correctly predict treatment for patients in the rofecoxib and combination treatment groups slightly more than expected. Correct rofecoxib and combination predictions by the study nurse were reportedly based mostly on side effects.

4. Discussion

The above results indicate that a gabapentin–rofecoxib combination provides significantly greater analgesia than single-agent gabapentin, but not rofecoxib, only for post-hysterectomy pain evoked by sitting. In addition to these limited differences, however, combination therapy significantly reduced pain at rest and pain evoked by peak expiration and cough at several postoperative timepoints during which either single-agent failed to distinguish from placebo. Thus, combination therapy appears to provide more consistent analgesia than either single agent which was further reflected in reduced pain interference scores and a small trend towards greater patient satisfaction. In fact, spontaneous and movement-evoked pain levels observed with gabapentin–rofecoxib combination treatment in this study are comparable to levels previously reported in epidural analgesic trials (Block et al., 2003). While all three treatments reduced cumulative morphine consumption, this reduction was significantly greater with the combination than with either single agent. Using pain as a primary outcome in the setting of patient-controlled analgesia can be problematic since opioids may be titrated, by patients in different treatment groups, to a common pain level. It is thus
notable that reduced pain and opioid consumption even further reinforce the antinociceptive effects of this combination. In fact, analysis of integrated analgesic assessment data, as initially proposed by Silverman et al. (1993), demonstrated greater separation between these four treatment groups and indicated that combination therapy is superior to single-agent gabapentin for pain at rest and all three measures of evoked pain. However, trends for separation between combination and rofecoxib failed to reach statistical significance and this could indicate somewhat less than a synergistic interaction between gabapentin and rofecoxib. Two previous laboratory investigations have been equivocal as to whether gabapentin interacts additively (Yoon and Yaksh, 1999) or synergistically (Hurley et al., 2002) with NSAIDs and the present trial certainly does not support synergy between gabapentin and rofecoxib. Regarding longer term analgesic effects, no differences in pain intensity were noted between any of the treatment groups one month after surgery, however, analgesic consumption was not assessed at this time point.

Based on observed adverse effect frequencies, this combination of gabapentin and rofecoxib appears to be safe in the context of postoperative pain management. However, it should be noted that these observations come from a population of patients with normal renal function and without coagulation defects or previous peptic ulcer disease. Furthermore, this trial was statistically powered to detect differences in pain intensity, not in adverse effect frequencies. Therefore, additional larger scale investigations would be needed in order to confirm the safety of this drug combination with greater certainty. Furthermore, it should be noted that rofecoxib was marketed in Canada with the broad labeled indication of pain in adults during the conduct of the presented trial. However, on September 30, 2004, Merck Sharp and Dohme announced a voluntary worldwide withdrawal of rofecoxib due to recent data suggesting increased risk of adverse cardiovascular event in patients taking the drug for longer than 18 months (Merck press release, 2004).

Peak expiratory flow, the one surrogate of pulmonary performance in this trial, was significantly higher with combination than with either single agent. This trial tracked PEF as a representative index of pulmonary function which we have shown to be highly correlated with movement-evoked pain (Gilron et al., 2002) and which has been successful in distinguishing the pulmonary effects of analgesic therapy following abdominal surgery (Hendolin et al., 1987). Although, pulmonary function indices are not thought to be predictive of postoperative respiratory complications (Ballantyne et al., 1998), postoperative changes in PEF often parallel those of forced expiratory volume in one second (FEV1) and forced vital capacity (Mason et al., 2001) and thus our findings may indicate a tendency towards accelerated pulmonary recovery.

Despite slight trends towards correct treatment predictions, blinding questionnaire data suggest overall that this trial was adequately blinded. The observation that combination therapy resulted in improvements of both subjective and objective measures further suggest that these results are unlikely due to bias.

Analgesic combination therapy has been pursued as a strategy for (1) improving analgesic efficacy, (2) reducing side effects and (3) reducing opioid requirements after surgery (Kehlet et al., 1999; Walker et al., 2002). While the specific benefits of a particular drug combination (e.g. improved efficacy versus reduced side effects) depend on the nature of their pharmacokinetic and pharmacodynamic interactions, it has been proposed that two drugs with distinct mechanisms and differing side effect profiles would comprise a favorable combination. This trial provides empiric evidence to support the clinical utility of a gabapentin-COX-2 inhibitor combination for postoperative pain. Future trials should further evaluate other analgesic combinations in order to enhance symptomatic improvement and functional recovery after surgery.

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