Analgesic Effects of Gabapentin on Post-hysterectomy Pain

— A Double-blind Study —

Keon Jung Yoon, M.D., Chang Sung Kim, M.D., Keon Hee Ryu, M.D.
Eun Sung Kim, M.D., Jong Ho Choi, M.D. Yoon Ki Lee, M.D.
and Dong Eon Moon, M.D.

Department of Anesthesiology, College of Medicine, The Catholic University of Korea, Seoul, Korea

Abstract

Background: The aim of the present study was to examine whether gabapentin, a new anti-epileptic agent with relatively low toxicities and side effects, could reduce postoperative pain.

Methods: Thirty-two patients scheduled for an elective total hysterectomy were investigated in this randomized, double blind, placebo-controlled study. The patients were randomized to receive either oral gabapentin 400 mg (gabapentin group, n = 16) or a matching placebo capsule (control group, n = 16) the night before and again 30 min before surgery as an adjunct to morphine patient-controlled analgesia (PCA). The visual analogue scale (VAS) for pain at rest and on movement, morphine consumption, overall satisfactions and postoperative side effects including sedation were recorded for 24 h after surgery.

Results: Total morphine consumption for 24 h after surgery was not significantly different between the two groups, but mean hourly morphine consumption during the period of 2 – 6 h after surgery was significantly greater in the control group. Movement VAS of gabapentin group measured at 6 h and 12 h after surgery was significantly lower than those of control group. There were no significant differences between the two groups with respect to the sedation score, patient’s satisfaction and the frequencies of side effects.

Conclusions: We observed that preoperatively administered oral gabapentin 800 mg reduced postoperative morphine consumption and incidental pain without increasing side effects. The addition of gabapentin to a morphine regimen may lower morphine consumption and provide better pain relief without increasing side effects. (Korean J Anesthesiol 2001; 41: S 13 – S 18)

Key Words: Anticonvulsant; gabapentin; Pain; postoperative.

INTRODUCTION

Gabapentin, an anticonvulsant structurally related to \( \gamma \)-aminobutyric acid (GABA), was recently reported to be effective not only in patients associated with neuropathy including reflex sympathetic dystrophy, postherpetic neuralgia and postsurgical neuropathy\(^1\) but also in animal models of neuropathic pains\(^2\). This drug also used in the adjunctive treatment of painful disorders including interstitial cystitis,\(^3\) vulvodynia,\(^7\) chronic daily headache\(^8\) and an acute arthritis model in rats.\(^9\) However, the analgesic effects of gabapentin on postoperative pain were not thoroughly evaluated.
There is only one article, which shows analgesic effect of gabapentin in a rat model of incision pain.

Opioids play a fundamental role in the management of postoperative pain, but their use is associated with a number of side effects, including nausea, vomiting, and respiratory depression. Besides, incidental pain due to movement renders pain control difficult because it requires high basal dosages or additional doses of opioids.

Gabapentin, a new anti-epileptic agent with relatively free of side effects at clinical doses, may possibly reduce use of narcotics and improve quality of analgesic effects.

We designed this randomized, double-blind, placebo-controlled study to evaluate the analgesic effect of preoperatively administered gabapentin on post-hysterectomy pain.

METHODS

After institutional review board approval, informed consent was obtained from each patient. Thirty-two ASA physical status I and II patients, 20–55 years old, scheduled for elective total hysterectomy, were enrolled in this double-blind placebo-controlled randomized study. Patients with a previous history of chronic pain, regular intake of analgesics, or psychiatric disorders were excluded.

Each patient was visited before operation and explained the aim of the study, the VAS and the use of the PCA pump.

Patients were assigned to receive gabapentin (Neurontin; Park-Davis Co., USA) 400 mg capsule (the gabapentin group, n = 16) or matching placebo capsule (the control group, n = 16) orally the night before and again 30 min before surgery in a double-blinded, randomized manner.

Anesthesia was induced with intravenous thiopental 5 mg/kg, and tracheal intubation was facilitated with IV succinylcholine 1 mg/kg. Anesthesia was maintained with enflurane and 60% nitrous oxide in oxygen. Paralysis was maintained with 4–6 mg of pancuronium and reversed with glycopyrrolate and pyridostigmine at the end of surgery.

Each patient in both groups received IV morphine 4 mg at the end of surgery and equipped with a 0.1% morphine contained PCA device (AP-II infusion pump, Baxter Healthcare Co., USA) with same PCA parameters for both groups (demand dose = 1 ml, lockout time = 6 min, no basal infusion). Assessments of resting and movement pain were made using VAS with a range of 0–10 indicating no pain and worst possible pain, respectively, at 2, 6, 12 and 24 h postoperatively. Sedation was assessed using a four-point scale (0 = alert, 1 = easily aroused by calling, 2 = aroused only by touch, 3 = difficult to arouse) and cumulative morphine consumption was checked at 2, 6, 12 and 24 h postoperatively also. Side effects such as nausea, vomiting, itching, dry mouth, dizziness, concentration difficulty and muscle weakness were recorded. Each patient was questioned about the overall satisfactions on the analgesic effects and the sleep during the 24 h after surgery.

Student’s t-test (demographic data, duration of surgery and cumulative doses of morphine), Mann-Whitney U-test (VAS, sedation scores, satisfaction scores) and chi-square test (side effects) were used for inter-group comparisons of data. P-values less than 0.05 were considered statistically significant.

RESULTS

Patient demographic data and duration of surgery were not different between two groups (Table 1). One patient in the control group was withdrawn from the trial as a result of programming errors, so that 31 patients were eventually studied. Total amount of morphine used during first 24 h postoperative period was not significantly different between two groups: 24.1 ± 9.9 mg in the gabapentin group and 32.7 ± 14.6 mg in the control group. But mean hourly morphine consumption during the period 2–6 h after surgery was significantly greater in the control group (Fig. 1).

Movement, but not resting, VAS of the gabapentin
Table 1. Demographic Characteristics, Duration of Surgery

<table>
<thead>
<tr>
<th></th>
<th>Age (yrs)</th>
<th>Weight (kg)</th>
<th>Duration of surgery (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin group</td>
<td>41.3 ± 6.1</td>
<td>55.7 ± 8.9</td>
<td>120.4 ± 21.8</td>
</tr>
<tr>
<td>Control group</td>
<td>44.0 ± 4.8</td>
<td>60.9 ± 7.6</td>
<td>129.3 ± 31.2</td>
</tr>
</tbody>
</table>

Values are mean ± SD. There were no significant differences between two groups. Gabapentin: received gabapentin 400 mg capsule orally the night before and 30 min before surgery, Control: received matching placebo capsule orally the night before and 30 min before surgery.

Fig. 1. Mean hourly consumption of morphine. Values are mean ± SD. Mean hourly consumption during 2–6 h was significantly greater in the placebo group (*P < 0.05).

Fig. 2. Postoperative pain (VAS) at rest and on movement for the 24 h after surgery. Values are mean ± SD. The movement VAS of the gabapentin group measured at 6 h and 12 h after surgery were significantly lower than those of the control group (*P < 0.05).

Fig. 3. Sedation score. Values are mean ± SD. There were no significant differences between two groups.

DISCUSSION

We have determined the analgesic effects of gabapentin in reducing pain attributed to operation after hysterectomy by conducting a double-blinded, placebo-controlled, randomized trial. Gabapentin reduced the mean hourly morphine consumption during the period 2–6 h after surgery and the incidental pain measured at 6 h, 12 h postoperatively without increasing side effects.

Previous studies, which have shown that gabapentin is inactive in the model of transient pain such as tail flick test and phase 1 of formalin test, suggest that gabapentin do not block physiological pain. However,
Table 2. Postoperative Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Gabapentin group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Nausea</td>
<td>7 (44%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (25%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Itching</td>
<td>0 (0%)</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>13 (81%)</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>13 (81%)</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10 (63%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Concentration difficulty</td>
<td>9 (56%)</td>
<td>9 (60%)</td>
</tr>
<tr>
<td>Muscle weakness</td>
<td>1 (6%)</td>
<td>3 (20%)</td>
</tr>
</tbody>
</table>

Values are the number of patients (%). There were no significant differences between two groups. Gabapentin: received gabapentin 400 mg capsule orally the night before and 30 min before surgery, Control: received matching placebo capsule orally the night before and 30 min before surgery.

gabapentin appears to be effective against hypersensitivity induced by not only acute tissue damage for example substance P-induced thermal hyperalgesia model, thermal injury model, and postoperative rat model, but also peripheral neuropath. This anti-hypersensitivity action of gabapentin is very different from morphine, which is analgesic and blocks both physiologic and clinical pain. Acute pain including postoperative pain is elicited by substantial injury of body tissue and activation of nociceptive transducers at the site of local tissue damage. Not only peripheral, but also central sensitization plays an important role in the post-injury hypersensitivity state found postoperatively. Central sensitization mainly results from the activation of NMDA receptors triggered by a barrage of nociceptive impulses from the periphery.

The exact mechanism of antinociceptive action of gabapentin is still unclear. But there were some evidences, which suggested that the voltage-dependent neuronal calcium channel and/or the glycine/NMDA-mediated events might be involved. NMDA antagonist has been known to inhibit central sensitization of the spinal dorsal horn neuron and therefore preemptively administered NMDA antagonist, such as ketamine has been suggested to reduce the dose requirement of morphine after operation and the morphine-related side effects. So, preemptively administered gabapentin also has the possibilities to have influence on the postoperative pain management.

In our present data, preemptively administered gabapentin reduced the mean hourly consumption of morphine during 2–6 h after surgery and the movement VAS measured at 6 h and 12 h postoperatively.

The reason why there was no significant difference in the mean hourly consumption of morphine during the period 0–2 h and 6–24 h after surgery is unclear but possibly due to relatively large initial bolus dose of morphine and short elimination half life of gabapentin estimated to be 5–6 h.

As suggested by Dahl et al., pain relief at rest is better than that during movement because the afferent input from the operative field at rest may differ from

Table 3. Satisfactions on Analgesia and Sleep

<table>
<thead>
<tr>
<th>Question</th>
<th>Gabapentin group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>How effective was your medication in relieving your pain?</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td>Excellent</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Good</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Satisfactory</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Poor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Very poor</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>What has been your quality of sleep during the last 24 h?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Much better than usual</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Better than usual</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Same as usual</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Worse than usual</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Much worse than usual</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Values are the number of patients. There were no significant differences between two groups. Gabapentin: received gabapentin 400 mg capsule orally the night before and 30 min before surgery, Control: received matching placebo capsule orally the night before and 30 min before surgery.
that during movement. Opioid alone can provide good analgesia at rest, but frequently gives poor pain relief during physiotherapy or movement. These results emphasize the necessities of non-opioid co-analgesics for the treatment of postoperative pain.

The movement VAS was measured for the evaluation of the effect of gabapentin on incidental pain and the present data suggest that gabapentin may have more analgesic effect on incidental pain than on resting pain.

While the effect of long-term administration of gabapentin cannot be predicted from this study, these data possibly suggest that repetitive co-administration of gabapentin may be clinically beneficial for sustained analgesia.

In summary, preoperatively administered oral gabapentin 800 mg reduced postoperative morphine consumption and incidental pain without any increase of side effects. Although morphine alone is a potent analgesics, its side effects may limit the use of higher doses and that may result in inadequate analgesia. The addition of gabapentin to a morphine regimen may lower the effective dose of morphine and provide better pain relief and fewer side effects. To determine the extent of the effectiveness of gabapentin for postoperative pain management, it is necessary to examine whether postoperative administration is effective and whether larger doses are more effective.

REFERENCES