THE EFFECTS OF PREOPERATIVE PREGABALIN ON POSTOPERATIVE ANALGESIA AND MORPHINE CONSUMPTION AFTER ABDOMINAL HYSTERECTOMY

ALİ EMAN1, AYTEN BİLİR2, SERBÜLENT GÖKHAN BEYAZ3
1Van İpêkyolu State Hospital, Department of Anesthesiology and Reanimation, Van - 2Eskisehir Osmangazi University Medical School, Department of Anesthesiology and Reanimation, Eskisehir - 3Sakarya University Medical School, Department of Anesthesiology and Reanimation, Sakarya, Turkey

ABSTRACT

Objectives: We aimed to evaluate the preemptive analgesic properties of pregabalin, an anticonvulsant drug used in clinical practice for the treatment of neuropathic pain.

Method: This study was performed on 40 patients from ASA I-II risk group aged 18-60 years which underwent total abdominal hysterectomy. Group I received 150 mg pregabalin and Group II was given a placebo in oral capsule form. Patient-Controlled Analgesia (PCA) morphine infusion was started. The time first bolus was used in the PCA system recorded as the first analgesic requirement time. Visual analog scale (VAS) scores, morphine consumption and side effects of all patients were recorded at 1, 4, 12 and 24 hours postoperatively.

Results: There was no difference observed in the first analgesic requirement time values between the two groups (p>0.05). A statistically significant decrease was observed in the VAS scores of the pregabalin group at 1, 4, 12 and 24 hours after surgery (p<0.005). Total morphine consumption in the pregabalin group was statistically significantly lower than in the control group at 8, 12 and 24 hours after surgery (p<0.005). No significant difference was observed between the two groups regarding side effects during the first postoperative 24 hours (p>0.05).

Conclusion: Our study demonstrated that a 150 mg pregabalin administered preoperatively is an efficient and safe agent for preemptive analgesia. Premedication with pregabalin reduces postoperative pain scores and total analgesic consumption without increasing sedation or other side effects in the postoperative period.

Key words: pregabalin; preemptive; postoperative; analgesia; morphine.

Received January 18, 2014; Accepted January 24, 2014

Introduction

Postoperative pain differs from other acute pains since it is expected and its cause is known in advance. Proper analgesia management increases patients’ postoperative well-being and reduces development of complications that can result in an extended hospital stay and increased costs(1). Currently, various methods are used for the management of postoperative pain. The most common of them are use of opioid analgesics, non-opioid analgesics and drugs from local anesthetics group applied using regional techniques(2).

In recent years, studies have shown that taking control over postoperative pain starting during the preoperative period is an important factor for reducing surgery-related stress, which brought about the idea of preemptive analgesia. It has been shown that noxious stimuli via afferent C fibers cause hyperexcitation in dorsal neurons of the spinal cord. The aim of the preemptive analgesia is to block postoperative pain by inhibiting this sensititation. Many different drugs such as paracetamol, lornoxicam, ketamine or gabapentin as well as regional blocks have been used for the purpose of preemptive analgesia(3-6).

Pregabalin is a gamma-aminobutyric acid (GABA) analogue. Previous studies have shown that pregabalin binds with high affinity to the α2-δ protein, found in the central nervous system’s voltage-gated calcium channels(7). Pregabalin inhibits the release of many neurotransmitters including glutamate, noradrenaline and P substance(8).
Currently, this agent is used for the treatment of neuropathic pain, along with its use for generalized and partial epilepsy\(^9\). Furthermore, many studies have shown that pregabalin can be used for the treatment of postoperative pain\(^1,2\).

In this study, we aimed to evaluate the preemptive analgesic activity of pregabalin in patients undergoing elective abdominal hysterectomy, considering abdominal surgery is a painful procedure with potential to generate central sensitization and peripheral hypersensitivity.

**Methods**

Written informed consent was obtained from the patients enrolled in this prospective, randomized, double-blind study in accordance with Eskisehir Osmangazi University Medical School Ethics Committee’s approval No: 2009/106 from 03.04.2009. Forty patients aged 18-60 years, from ASA I-II group scheduled for total abdominal hysterectomy surgery under general anesthesia were included in the study. Patients with known renal, hepatic, pulmonary or cardiovascular system’s problems, drug or alcohol addiction, history of allergy and obese patients were excluded from the study.

Non-premedicated patients were kept fasting for 8 hours prior to the surgery and randomized into two groups using the sealed envelope method.

Group I (n=20) received 150 mg of oral pregabalin and Group II (n=20) oral placebo capsule, both given 60 minutes prior to the surgery. Patients admitted to the operating hall were monitored for electrocardiography (ECG), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR) and peripheral oxygen saturation (SpO\(_2\)). These parameters were recorded pre-induction, post-induction, 1, 5, 30 and 60 minutes after intubation and after extubation.

Anesthesia for both groups was induced with thiopental, 5-7 mg/kg and vecuronium 0.1 mg/kg. Sevoflurane 1-3%, and a mixture of 50% N\(_2\)O in O\(_2\) were used for the maintenance of anesthesia for intubated patients. In the event that additional analgesia was required remifentanil, a neuromuscular blocker was required a proper dose of vecuronium. At the conclusion of the surgery, a neuromuscular block was antagonized with neostigmine 0.04 mg/kg and 0.5 mg atropine and shortly before extubation 3 mg morphine was given intravenously to both groups. The duration of anesthesia and duration of surgeries were recorded.

All patients were transferred to the postoperative care unit and when the Aldrete recovery score (ARS) (10) reached 9, morphine infusion was started using the patient-controlled analgesia method. Morphine 50 mg was added into 100 ml of normal saline. Initial settings of the Patient-Controlled Analgesia (PCA) device were as follows: bolus dose 1 mg, lockout interval 10 minutes and a 4-hour limit 40 mg. The time first bolus used in the PCA system was recorded as the first analgesic requirement time.

All patients’ SBP, DBP, MBP, HR, SpO\(_2\), Visual analog scale (VAS) scores, Ramsay Sedation Scale values (RSS), total morphine consumption and side effects (nausea, vomiting, increase in oral secretion, nightmares, double vision, hallucination, agitation) were recorded at 1, 4, 8, 12 and 24 hours after the point when the ARS reached 9. Patients with complaints of severe nausea and vomiting were treated with 10 mg of intravenous metoclopramide.

**Statistical analysis**

The results obtained in the study were evaluated using the SPSS (Statistic Package for Social Sciences) program, version 13.0. Along with descriptive statistics methods (mean value and standard deviation), the Kolmogorov-Smirnov test for the comparison of quantitative data showed normally distributed and abnormal data. The tests used were as follows: for the comparison of normally distributed parameters, an independent t-test; for abnormally distributed parameters, a Mann Whitney-U test; for qualitative data, a Chi-square test; and for the comparison of postoperative morphine consumption, a Two Way Repeated Measures ANOVA (One Factor Repetition) test. Results were expressed as mean ± standard deviation. While the p-value < 0.05 was considered statistically significant, the p-value < 0.005 was accepted as highly significant.

**Results**

No statistically significant difference was found between the groups regarding patients demographic data, duration of the surgeries and the anesthesia (p>0.05, table 1). Patients were monitored in the recovery room for the first hour after the surgery and when the ARS reached 9. PCA morphine infusion was started. A comparison of patients’ first analgesic requirement times showed that patients from the pregabalin group had a delayed analgesic requirement; however, this difference was not statistically significant (p=0.2, respectively, 30.75 ± 8.77 min, 27.0 ± 10.97 min).
There was no statistical difference between the two groups regarding hemodynamic parameters recorded intraoperative and postoperative in given time intervals (p>0.05).

Postoperative VAS values recorded after 1 hour were comparable in both groups of patients (p>0.05). However, a decrease of the VAS values recorded after 4, 8, 12 and 24 hours in the pregabalin group compared with the placebo group was found to be highly significant statistically (p<0.005, figure 1).

Postoperative PCA administered total morphine consumption at 8, 12, and 24 hours was significantly lower in the pregabalin group compared with the placebo group (p<0.005, figure 1).

All patients were asked about side effects 24 hours after the surgery. Three patients from Group I (15%) and 4 patients from group II (20%) reported nausea. Additionally, pruritus was seen in one patient from Group I.

No statistically significant difference was observed between the groups in the postoperative period regarding the Ramsay Sedation Scale score (p>0.05).

Table 1: Demographic data.
*: p>0.05 not statistically significant

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>p*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>43.45 ± 11.56</td>
<td>42.15 ± 11.12</td>
<td>0.71</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>66.30 ± 6.7</td>
<td>64.30 ± 6.07</td>
<td>0.32</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>165.95 ± 8.19</td>
<td>161.70 ± 5.95</td>
<td>0.68</td>
</tr>
<tr>
<td>Anesthesia time (minute)</td>
<td>113.75 ± 35.54</td>
<td>124.50 ± 43.29</td>
<td>0.40</td>
</tr>
<tr>
<td>Operation time (minute)</td>
<td>101.20 ± 33.40</td>
<td>113.35 ± 41.45</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 2: Comparison of postoperative morphine consumption between groups by time.
Data is shown as mean ± standard deviation, *: p<0.005 Statistically significant.

<table>
<thead>
<tr>
<th>Time</th>
<th>Group 1</th>
<th>Group 2</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Hour</td>
<td>1.85 ± 0.67</td>
<td>2 ± 0.91</td>
<td>0.8</td>
</tr>
<tr>
<td>4. Hour</td>
<td>6.9 ± 2.5</td>
<td>8.9 ± 1.4</td>
<td>0.08</td>
</tr>
<tr>
<td>8. Hour</td>
<td>10.4 ± 3.7</td>
<td>16.9 ± 1.9</td>
<td>0.0001*</td>
</tr>
<tr>
<td>12. Hour</td>
<td>13.2 ± 4.5</td>
<td>23.3 ± 2.4</td>
<td>0.0001*</td>
</tr>
<tr>
<td>24. Hour</td>
<td>19.9 ± 6.5</td>
<td>35.1 ± 5.5</td>
<td>0.0001*</td>
</tr>
</tbody>
</table>

Discussion

The present study showed that premedication with pregabalin reduces postoperative pain scores and analgesic consumption after abdominal hysterectomy without increasing sedation or other side effects.

According to recent evidence, along with the use of gabapentin and pregabalin as effective analgesics in patients with neuropathic pain or chronic pain syndrome, preemptive administration of these drugs provides effective postoperative analgesia(8,12). Many studies showed that these anticonvulsants could increase the analgesic effects of morphine, non-steroidal anti-inflammatory drugs and COX-2 inhibitors(8,13).

Recent studies have shown that pregabalin exhibits a significant analgesic effect in acute postoperative pain as well(14). In a study by Hill et al(14) performed on patients undergoing oral surgery under local anesthesia, 300 mg of pregabalin resulted in a longer duration of analgesia and it was a more efficient pain reliever after dental extraction than 400 mg of ibuprofen. Additionally, a combination of the two drugs was reported as the most effective therapy.

In this study, we aimed to evaluate the preemptive analgesic activity of pregabalin in patients undergoing elective abdominal hysterectomy, considering abdominal surgery to be a painful procedure with potential to generate central sensitization and peripheral hypersensitivity. A preoperative 150 mg of pregabalin and a loading dose of morphine administered 15 minutes before the end of the surgery were given to the patients. VAS values recorded at 4, 8, 12 and 24 hours were lower in the pregabalin group compared with the placebo group. When morphine consumption between the two groups was compared,
it was seen that morphine consumption at 4, 8, 12 and 24 hours was lower in the pregabalin group compared with the placebo group. Comparison of the results of the two groups showed a significant fact that VAS values and the morphine consumption decreased simultaneously.

Although the first analgesic requirement times of the patients given pregabalin were longer then in the placebo group, this difference was not found to be significant statistically. The first analgesic requirement time values obtained in this study were found to be similar to those in two different studies on preoperative pregabalin effects by Jokela et al (15, 16). No difference was observed between the two groups hemodynamic parameters preoperative, intraoperative, or postoperative in this study.

Agarwall et al (17), who worked with laparoscopic cholecystectomy patients, used preoperative pregabalin in a similar way to our study and obtained parallel results. Hemodynamic data were rarely referred to in similar studies (15,16). The reason for this could be the fact that these studies were primarily focused on preemptive analgesia, postoperative analgesia, postoperative VAS values and analgesic consumption or a lack of a significant difference between hemodynamic parameters. However, it should not be forgotten that hemodynamic data can be helpful in the evaluation of pain and adequacy of anesthesia and that pain can increase the stress response in the risk groups.

In a study by Jokela et al (15), patients undergoing gynecologic laparoscopic surgery were given 5 mg of diazepam, 75 mg and 150 mg of pregabalin and postoperative acetaminophen, codeine and ibuprofen. It has been shown that the quality of anesthesia was better and that VAS values decreased more in the group that had been given 150 mg of pregabalin than in the group that had been given 75 mg of pregabalin and the control group. Despite this, 150 mg of pregabalin did not reduce the amount of postoperative analgesics required. Analgesics used in this study are less potent then the morphine that was used and the use of stronger analgesics can affect analgesic efficacy and analgesic consumption. Additionally, the reason this study’s results are different than results we obtained could be the fact that while they used the laparoscopic method with different postoperative pain mechanisms, patients in our study underwent laparotomy.

In another study by Jokela et al (16), patients undergoing laparoscopic hysterectomy were given preoperative diazepam and pregabalin (150 mg and 300 mg pregabalin group) with a pregabalin dose repeated 12 hours after the surgery. Results showed a similar effect to diazepam and 300 mg of pregabalin on VAS values and oxycodone consumption. The group given 600 mg of pregabalin had significantly lower VAS values and analgesic consumption. According to the results of this study, higher pregabalin doses are connected with increased incidence of adverse effects.

Schulmeyer et al (18) reported significant decreases in VAS values and morphine consumption at 24 hours after surgery in the patients who underwent laparoscopic sleeve gastrectomy who received one preoperative dose of 150 mg of pregabalin. Similarly, Agarwall et al (17) reported significant differences in postoperative VAS values and PCA fentanyl consumption of the laparoscopic cholecystectomy patients premedicated with 150 mg of pregabalin. Findings that pregabalin in a 150 mg dose does not increase incidence of adverse effects and increases analgesic effects are in accordance with our study as well.

Pregabalin is an easily tolerated drug with limited side effects and low potential for interaction with other drugs. Different studies reported side effects such as somnolence, dizziness, confusion, headache, ataxia and weight gain (19). Whereas most of these side effects were reported for chronic use, the most common side effects for postoperative patients were dizziness, somnolence and sedation. In our study, except for nausea and pruritus, no side effects were reported. Additionally, no statistically significant difference was observed between the two groups regarding evaluation of sedation.

The majority limitation of this study is inadequate number of both patient group and control group. Additionally, preoperative pregabalin given different times and preoperative pregabalin’ different doses that 50, 75, 150 and 300 mg are need to be randomized controlled trails.

In conclusion, this study has shown that preoperative pregabalin can be used for preemptive analgesia. We believe that in order to achieve optimal postoperative analgesia, further studies evaluating the continued use of pregabalin in the postoperative period or the use of multiple doses preoperatively would be useful.
References


Acknowledgements
We thank all patients that agreed to participate in this study.

Request reprints from:
Dr. SERBÜLENT GÖKHAN BEYAZ, Associate Professor
Sakarya University Medical School
Merkez Campus, Anesthesiology, Adapazarı, Sakarya
Republic of Turkey