The Effects of Gabapentin on Acute and Chronic Postoperative Pain After Coronary Artery Bypass Graft Surgery

Alper Ucak, MD,* Burak Onan, MD,* Huseyin Sen, MD,† Ismail Selcuk, MD,* Alpaslan Turan, MD,‡ and Ahmet Turan Yılmaz, MD*

**Objectives:** The purpose of this study was to evaluate the analgesic effects of perioperative gabapentin on postoperative acute and chronic pain after coronary artery bypass graft (CABG) surgery with median sternotomy and internal mammary artery harvesting.

**Design:** A double-blind randomized clinical study.

**Setting:** A single-academic hospital.

**Participants:** Patients with ischemic heart disease who were scheduled to undergo CABG surgery.

**Interventions:** Forty patients were allocated randomly into 2 groups; the gabapentin group (n = 20) received 1.2 g/d of oral gabapentin before and for 2 days after surgery, and the placebo group (n = 20) received a placebo capsule instead. The primary outcome was to evaluate the effects of gabapentin on acute and chronic pain after surgery. The postoperative evaluation included the assessment of pain at rest and when coughing, intravenous tramadol usage, postoperative morbidities, and side effects of gabapentin. Postoperative analgesia at 6, 12, 18, 24, 48, and 72 hours after extubation and at discharge was evaluated with the visual analog scale. The assessment of postoperative pain at the 1- and 3-month follow-ups was performed using a numeric rating scale.

**Main Results:** Postoperative pain scores at 1, 2, and 3 days were significantly lower in the gabapentin group when compared with the placebo group (p < 0.05). Pain scores at 1 and 3 months postoperatively were lower in the gabapentin group than in the placebo group (p > 0.05). Consumption of intravenous tramadol given as rescue analgesia within 24 hours after extubation in the gabapentin group was 99.0 ± 53.8 mg versus 149.4 ± 72.5 mg in the placebo group (p < 0.05). There were no differences in the incidence of side effects and time to extubation between the groups.

**Conclusions:** Gabapentin significantly reduced the intensity of pain and tramadol consumption in the early postoperative period after CABG surgery. Pain scores at 1 and 3 months after surgery were low in both groups, with no significant difference between the groups.

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**KEY WORDS:** gabapentin, postoperative pain, cardiac surgery, coronary artery bypass graft surgery

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From the Departments of *Cardiovascular Surgery and †Anesthesiology and Reanimation, GATA Haydarpasa Education Hospital, Istanbul, Turkey; and ‡Department of Outcomes Research, The Cleveland Clinic, Cleveland, OH.

Address reprint requests to Alper Ucak, MD, Department of Cardiovascular Surgery, GATA Haydarpasa Education Hospital, Tibbiye Cad., Uskudar, 34668-Istanbul, Turkey; E-mail: draisperucak@gmail.com

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**C**oronary artery bypass graft (CABG) surgery is indicated to increase quality of life by reducing symptoms such as anginal pain. However, pain after CABG surgery may persist well after wound healing has taken place, and in some patients, chronic pain persists for several months.1 The reported incidence of chronic pain after cardiac surgery varied from 21% to 56%.2-5 Of those patients, 33% to 66% experienced chronic pain lasting more than 3 months, and 25% to 33% experienced more than 1 year of chronic pain.6 It has been noted that chronic pain is more common than other morbidities of cardiac surgery such as mediastinitis, renal dysfunction, and neurologic deficits.7,8 This persistent pain can be severe enough to interfere with daily activities and quality of life and often has an adverse effect on mood for patients.

Postoperative pain after cardiac surgery is different from the cardiac anginal symptoms experienced before CABG surgery. There are different theories to elucidate the underlying mechanism for chronic pain. They include entrapment neuropathy associated with sternal or rib retraction, musculoskeletal trauma during surgery, sternal dehiscence or nonunion, harvesting the internal mammary artery (IMA) with cautery, fractured ribs, painful sternal wires, and postoperative infection.9 In particular, manipulation of the sternum and IMA harvesting from the chest wall by using electrocautery may cause an iatrogenic injury to the intercostal nerves and associated neuralgia or neuropathy.9,10

Postoperative pain management in cardiac surgery encompasses different analgesic drugs including acetaminophen, nonsteroidal anti-inflammatory drugs, local anesthetics, and opioids. Despite all these medications, analgesia can be unsatisfactory. Because CABG surgery involving sternotomy and IMA harvesting can be associated with nociceptive and neuropathic pain after surgery, alternative agents such as gabapentin that prevent neuropathic pain syndromes may allow the relief of noncardiac symptoms associated with surgical trauma.

Gabapentin has been effective in treating various neuropathic pain syndromes.11 This drug exerts a selective effect on the nociceptive process by inhibiting central neuronal sensitization. It also produces antihyperalgesia by decreasing excitatory amino acid neurotransmission in the spinal cord through a direct postsynaptic or presynaptic inhibition of Ca²⁺ influx.12 It has been shown that gabapentin reduced pain scores and opioid requirements in different surgical settings.13,14 To date, there have been a few published reports on the use of gabapentin in cardiac surgery.15-18 These studies showed that gabapentin effectively reduced postoperative pain and the need for additional analgesics in the early postoperative period. However, Rapchuk et al18 failed to find any pain reducing properties of gabapentin in cardiac surgery. There have been no studies reporting the effects of gabapentin on chronic pain. Therefore, the objective of this prospective randomized study was to investigate the effects of gabapentin on the intensity of acute and chronic postoperative pain after CABG with median sternotomy and left IMA harvesting.
METHODS

After obtaining approval of the Institutional Ethics Committee and written informed consent, 40 patients (34 men and 6 women) who were less than 80 years of age and undergoing elective CABG surgery with cardiopulmonary bypass (CPB) were enrolled in this study. The study population was selected from 96 patients who underwent CABG surgery during the same period. Patients with an ejection fraction less than 50%, obstructive lung disease, renal insufficiency (preoperative creatinine level $>2.0$ mg/dL), a known allergy to any of the study medications, a height of less than 145 cm, a weight of more than 100 kg, a history of alcohol or drug abuse, and neurologic dysfunction were excluded to avoid gabapentin-related events after surgery. Patients receiving medications that may have an adverse effect on the evaluation of postoperative analgesia such as chronic nonsteroidal anti-inflammatory drugs or tranquilizers were excluded from participating in the study. Patients who were unable to express themselves verbally or who were unable to fill out the questionnaires also were excluded. At the preoperative evaluation the day before surgery, the surgical procedure, postoperative care, and visual analog scale (VAS) were explained to all participants.

The patients were assigned randomly into 2 groups (using a computer-generated table) consisting of 20 patients in each. In the gabapentin group (group 1), the patients received oral gabapentin, 1.2 g/d (Neurontin; Pfizer, Goedecke GmbH, Germany), before and 2 days after surgery, and the placebo group received a placebo capsule instead. The initial dose of the study medication was administered 1 hour before surgery. The same dose regimens were administered orally on the 1st and 2nd postoperative days. A single nurse who was blinded to the study protocol prepared the placebo capsules and administered them to the patients. The doctors and nurses in the operating room, intensive care unit, and ward were blinded to the study protocol.

All patients received premedication with 0.1 mg/kg of diazepam intramuscularly 45 minutes before surgery. All the staff in the operating room was unaware of the randomization. The induction of general anesthesia was achieved by using midazolam (0.1 mg/kg), fentanyl (5 µg/kg), vecuronium (0.1 mg/kg), and propofol (0.5 mg/kg). The maintenance of anesthesia was provided with fentanyl, midazolam, sevoflurane, and a 50% mixture of air and oxygen. Additional bolus doses (100-250 µg) of fentanyl were given during surgery if needed. Fentanyl and morphine were not administered in the postoperative course.

Surgical procedures were performed through standard median sternotomy. The same surgeon, who was blinded to the study protocol, performed all operations with the same technique. Operations involved harvesting of the left IMA after opening the left pleura and saphenous veins from the calf using a standard open incision. The left IMA was harvested by using cautery and a chest retractor on 1 side of the sternum. CPB was conducted using a membrane oxygenator and roller pump. Blood pressure was kept between 50 and 70 mmHg during CPB, and intravenous ephedrine was used if it decreased below 50 mmHg. Antegrad intermittent blood cardioplegia at 32°C was used. The patients were cooled to 32°C and then warmed to 36.5°C before weaning from CPB and decannulation. Dopamine was used as the first choice of inotropic agent. In all patients, a 32F thoracic chest tube was placed into the left hemithorax through the 6th intercostal space in the anterior axillary line, and one 32F mediastinal tube was passed below the xiphoid area. These tubes were always removed within 24 hours of the operation. The sternotomy was closed with 6 separate sternal wires, and the skin incision was closed with intracutaneous stitches. After surgery, the patients were transferred to the intensive care unit (ICU) and immediately extubated when the peripheral temperature exceeded 36.5°C. A single anesthesiologist, who was blinded to the study protocol, determined the criteria for extubation.

Postoperative analgesia was evaluated during rest and when coughing by using the VAS (ranging from 0 to 10) at 6, 12, 18, 24, 48, and 72 hours after extubation and at discharge. The VAS consisted of a 10-cm line anchored at 1 end by a label such as “no pain” and at the other end by a label such as “worst pain imaginable” or “pain as bad as can be.” Patients who had a VAS score of at least 4 during the first 24 hours after extubation were given 1 mg/kg of tramadol intravenously for analgesia. After the first 24 hours of operation, during the 1st and 2nd postoperative days, all patients had 50 mg of oral tramadol every 12 hours and 500 mg of paracetamol (acetaminophen) every 8 hours. During this period, 1 mg/kg of intravenous tramadol was delivered as the rescue medication if the VAS score was above 4. After the first 72 hours, 500 mg of paracetamol were given orally every 8 hours. It was recommended that patients take paracetamol after discharge from the hospital. Nausea and vomiting were recorded, and intravenous ondansetron (4 mg) was administered for treatment.

All patients completed a 1- and 3-month follow-up. The assessment of postoperative pain at 1 month was performed at the outpatient visits, and at 3 months it was carried out via telephone with a 10 point numeric rating scale; 0 indicated “no pain,” and 10 indicated the “worst pain imaginable.” Patients who had a numeric rating scale score of more than 0 were further evaluated with regard to the impact of pain on their daily activities. Patients were allowed to take acetaminophen on demand.

The same cardiovascular surgeon, who was blinded to the study groups, recorded all measurements, the visual analog score (at rest and with cough), and the cumulative consumption of tramadol. The postoperative hemodynamic status with regard to ventricular function was observed. Postoperative morbidities such as atrial fibrillation, atelectasis, renal failure, pleural effusion, drainage from chest tubes, and sternal dehiscence were analyzed. In addition, the presence of any side effects (eg, nausea and vomiting) related to gabapentin was assessed after surgery.

The initial sample size estimation showed that approximately 18 patients were needed in each group to detect a clinically relevant reduction of the level of pain by 25%, with a power of 0.80 and a level of significance of 5%. Statistical analysis was performed with SPSS for Windows version 15.0 (SPSS Inc, Chicago, IL). Data were expressed as mean (standard deviation) or the number (%) of patients. All variables were tested for normal distribution by Kolmogorov-Smirnov test. The Student t test, Mann-Whitney U, and chi-square tests were used for comparison of the means of normally distributed data. For repeated measures, analysis of variance tests were performed to evaluate the effect of gabapentin versus placebo over time. Bonferroni correction was performed to compensate for the possible effects of repeated testing. Sphericity was evaluated by using the Mauchly Test of Sphericity. Significance was determined at a $p$ value less than 0.05.

RESULTS

Patient demographics and perioperative data were similar between the groups (Tables 1 and 2). Postoperative pain scores of patients in the early postoperative period are depicted in Figures 1 (in the resting position) and 2 (with cough). The mean pain scores (at rest and with cough) at 6, 12, 18, 24, 48, and 72 hours after extubation; at discharge; and at 1 and 3 months were lower in the gabapentin group than the placebo group. The visual analog scores (at rest and with cough) recorded during the first 3 days after surgery showed a statistically significantly decrease in the gabapentin group when compared with the placebo group. Results of the gabapentin group were better than the placebo group by repeated-measures analysis of variance test. The groups satisfied the sphericity assumption according to the Mauchly Test of Sphericity.
Considering the intensity of chronic postoperative pain, the mean pain scores with cough and at rest at 1 month and 3 month postoperatively were low in both groups at about the same level as at discharge, with no intergroup difference (Fig 3). With regard to the incidence of chronic pain, 7 (35%) patients from group 1 and 9 (45%) patients from group 2 declared that they suffered from pain at 3 months after surgery.

Postoperative analgesic (tramadol) consumption of patients within the first 24 hours after extubation was significantly lower in the gabapentin group when compared with the placebo group (99.0 \pm 53.8 mg vs 149.4 \pm 72.5 mg, \( p < 0.05 \)) (Table 2). Intraoperative fentanyl consumption, mechanical ventilation time, and hospital stay were similar between the groups (Table 2).

Minor side effects are summarized in Table 3. Side effects were diagnosed in 8 (40%) patients in the gabapentin group and 5 (25%) patients in the placebo group. Although minor side effects were found higher in the gabapentin group, there was no statistically significant difference when they were compared with the placebo group (\( p > 0.05 \)). The most common side effects of gabapentin during the study period were nausea/dyspepsia (20%) and vomiting (20%), followed by dizziness (15%). No patient discontinued the use of gabapentin because of its side effects.

There was no mortality, and therefore all patients were able to complete the study protocol. No patient needed a high dose of inotropic support after weaning from CPB. There were no differences in postoperative morbidities between the groups. Postoperative complications in groups 1 and 2 included atrial fibrillation (3 vs 6 patients), atelectasis (2 vs 3 patients), and pleural effusion (1 vs 2 patients). Only 1 patient in the gabapentin group had a superficial wound infection and treatment.

**DISCUSSION**

Several studies have been performed with gabapentin use in cardiac surgery.\(^{15-18}\) This study investigated the effect of gabapentin treatment on the intensity of postoperative acute and chronic pain in patients undergoing CABG surgery.
through median sternotomy with left IMA harvesting. There were 3 main findings in the present study: (1) perioperatively administered gabapentin significantly decreased the intensity of acute pain (at rest and with cough) during the first 24 hours and at 2 and 3 days after surgery, (2) the amount of tramadol consumption within 24 hours after extubation was significantly lower in the gabapentin group, and (3) perioperative use of gabapentin did not have a significant effect on postoperative pain scores at 1 and 3 months after surgery compared with the placebo group. These results indicate that perioperative gabapentin treatment can be effective to decrease pain in the early postoperative period.

Postoperative pain after cardiac surgery typically is regarded as nociceptive pain related to stimulation of peripheral mechanoreceptors during surgery. Meyerson et al. noted that cardiovascular operations performed through a sternotomy incision could lead to postoperative pain because of sternal retraction. Sternal retraction stretches the nerves at the costovertebral junctions, and this may cause brachial plexus injury. Nevertheless, Conacher et al. noted that dissection of the IMA from the chest wall could damage the intercostal nerves. Sternal wires and chest tubes placed through intercostal spaces can lead to surgical damage to the anterior ramie of the intercostal nerves and stimulation of the peripheral nerve endings. Mailis et al. reported that anterior intercostal nerve damage occurred in 73% of patients undergoing CABG surgery with IMA harvesting, and 15% of them experienced chronic chest wall pain 5 to 28 months after surgery. In this study, the authors studied a relatively homogenous patient population with ischemic heart disease. All patients underwent CABG surgery through median sternotomy with left IMA harvesting performed by using cautery; the authors believed that this type of procedure could be associated with postoperative neuropathic pain. Therefore, gabapentin was used to assess its effects on this type of pain after CABG surgery.

The potential role of anticonvulsants in neuropathic pain syndromes has been noted. Gabapentin, an anticonvulsant, is effective in the treatment of these syndromes; however, its mechanism of action is not completely clear. Gabapentin inhibits central neuronal sensitization, which is considered an important determinant of chronic neuropathic pain after trauma and surgery. The reduction of central sensitization by an antihyperalgesic drug like gabapentin may reduce acute postoperative pain. Another potential effect of gabapentin is the reduction of excitatory amino acid neurotransmission in the spinal cord induced by tissue injury. Therefore, gabapentin can be a choice in the treatment of acute and chronic postoperative pain.

The effects of gabapentin on early postoperative pain after cardiac surgery have been reported in recent studies. Parlow et al. showed that gabapentin (600 mg orally once before surgery) was beneficial to reduce pain scores on postoperative day 1 after cardiac surgery. The authors noted that pain scores in their study were lower than previously reported studies. In addition, the authors reported that the blood level of gabapentin remained constant throughout and after CPB. This shows the stability of gabapentin concentration in blood and may affect its pharmacodynamics and selection of an optimal dose. Therefore, the preoperative use of gabapentin to reduce postoperative pain is not limited by CPB in cardiac surgery. In the other recent study by Menda et al., a preoperative 600-mg single dose of gabapentin significantly decreased postoperative pain scores at rest and with cough, and total morphine consumption during 48 hours after cardiac surgery. The present study protocol was different from these studies in the following ways: (1) the authors gave gabapentin for 3 consecutive days starting before surgery, (2) the dose of gabapentin was relatively higher, (3) tramadol was used instead of other opioids such as morphine to avoid sedation, and (4) patients were followed during their hospital stay and at 1 and 3 months after surgery. In the present study, the difference in pain scores reached a statistical significance by the 6th hour after extubation, and this persisted on the 1st and 2nd postoperative days. This finding might be related to continuous delivery of gabapentin for 3 consecutive days. Moreover, postoperative consumption of tramadol within the first 24 hours after surgery was significantly lower in the gabapentin group. On the other hand, Rapchuk et al. recently described an identical gabapentin dosing regimen (1.2 mg/d orally) to the present study. However, the authors failed to find any analgesic-reducing properties of gabapentin in the early postoperative period as have

Fig 3. Postoperative chronic pain scores (mean ± standard deviation) in the resting position and when coughing versus time (analysis of variance tests with Bonferroni correction).

Table 3. Incidence of Side Effects Encountered Throughout the Study in the Gabapentin and Placebo Groups

<table>
<thead>
<tr>
<th>Side Effect</th>
<th>Group 1 Gabapentin (n = 20)</th>
<th>Group 2 Placebo  (n = 20)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea/dyspepsia</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>2</td>
<td>NS</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Constipation</td>
<td>1</td>
<td>1</td>
<td>NS</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Headache</td>
<td>1</td>
<td>0</td>
<td>—</td>
</tr>
</tbody>
</table>

NOTE. Data are presented as the number of patients.
been described in other articles. The difference between the present results and those of Rapchuk et al, considering the analgesic effect of gabapentin in the early postoperative period, could be related to the surgical technique or management of patients in the perioperative period. Rapchuk et al used fentanyl in the first 48 hours postoperatively, which is in contrast to the present study protocol.

Chronic postoperative pain has been recognized as a severe and frequent adverse outcome after many surgical procedures including amputation, inguinal hernia surgery, breast surgery, gall bladder surgery, and lung surgery. In particular, of patients undergoing CABG surgery, up to 66% experience chronic pain lasting more than 3 months.6 In approximately one-third of the patients with coronary revascularization, the chronic pain syndrome may disturb the quality of life, interfere with sleep, and reduce the work performance of the patients.7 In the present review, the efficacy of gabapentin on long-term pain during 1 to 3 months has been studied in only 5 trials.13 These studies included different surgical procedures and perioperative dose regimens between 1,200 and 1,600 mg for gabapentin. There was a wide variation in the number of patients and the duration of treatment (between 2-10 days). No prospective study to date has noted the effect of perioperative gabapentin treatment on pain scores at 1 and 3 months after CABG surgery despite the fact that the scores were low compared with those recorded during the hospital stay. These results might be related to the decreased incidence of postoperative pain in CABG procedures. Pain scores also were low in the placebo group. Thus, further studies with a high number of patients are necessary to elucidate the efficacy of perioperative gabapentin on chronic pain after cardiac surgery. According to the literature review, only 1 study has explored the effects of gabapentin on the treatment of chronic pain in cardiac surgery. Bıyık et al17 recently studied the effects of gabapentin in patients with chronic pain persisting 3 months or more after cardiac surgery. The authors showed that daily treatment with gabapentin for 30 days was effective in chronic pain without obvious side effects. They also showed that gabapentin was superior to daily diclofenac potassium, a nonsteroidal anti-inflammatory drug. Considering the study of Bıyık et al, it might be interesting to show the efficacy of continuous daily treatment with gabapentin delivered postoperatively in a prospective study.

In the present study, it was observed that gabapentin had a favorable side effect profile in the postoperative period. Although 40% of patients experienced at least 1 minor side effect after surgery, no patient discontinued the treatment. Previous studies including a single dose of gabapentin in cardiac surgery did not report serious side effects.15-17 In the present study, nausea and vomiting were the most frequent side effects, each presenting with an incidence of 20% and treated successfully, which is similar to previous studies.16,22 Menda et al16 reported that nausea was the common side effect after cardiac surgery, but the authors noted that morphine used postoperatively could mask drug-related morbidities. Similarly, it should be noted that tramadol was used as an additional analgesic agent to relieve the pain if needed. Tramadol generally is well tolerated, but it also may cause nausea, dizziness, headache, drowsiness, and vomiting. Therefore, the use of tramadol might have increased the incidence of potential side effects of gabapentin in this study.

Several pain medications including fentanyl and acetaminophen were used in all patients. Fentanyl was used to provide the induction and maintenance of general anesthesia, and additional bolus doses were given during the procedures. The authors observed that there was no significant difference between groups in the doses of fentanyl used during the procedures. The use of fentanyl after surgery might affect the need for additional analgesic within the first 24 hours after extubation and might cause a decrease in the use of additional analgesic agents such as tramadol or morphine. Therefore, the authors did not give this agent in the postoperative course of patients to avoid bias.

Study limitations included a small number of patients undergoing CABG surgery with sternotomy and left IMA harvesting and the deficiency of appropriate dose regimens from the literature for gabapentin in the perioperative period to decrease acute or chronic pain of cardiac surgery. In this study, tramadol was used as the rescue analgesic. Because most similar studies have used morphine as the rescue analgesic, a comparison to previous data becomes more complicated. Nausea and vomiting are common side effects of tramadol, especially if given intravenously, and this might mask similar effects of gabapentin. In addition, a validated and specific chronic pain measurement tool could be used for the outcome.

In conclusion, in this study, gabapentin (1.2 g/d) treatment before and for 2 days after CABG surgery had a beneficial effect on the management of postoperative acute pain and decreased the need for additional analgesia delivery after surgery. Although postoperative pain scores were low at 1 and 3 months after CABG surgery, the authors did not find a significant effect of perioperative gabapentin on chronic postoperative pain. Further studies with a higher number of patients are necessary to evaluate the efficacy, optimal dosing, and adverse effects of gabapentin in the setting of cardiac surgery.

REFERENCES