

Analgesic Effects of Gabapentin after Spinal Surgery

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Background: A combination of opioid and nonopioid analgesic drugs may improve the quality of postoperative analgesia as well as reduce opioid requirements and their associated side effects. Studies have shown synergism between gabapentin and morphine in animal and human experiments and in the treatment of incisional pain. Therefore, the authors investigated, in a randomized, placebo-controlled, double-blind study, the effects of gabapentin on acute postoperative pain and morphine consumption in patients undergoing spinal surgery.

Methods: After standard premedication, 25 patients in the control group received oral placebo, and 25 patients in the gabapentin group received 1,200 mg of gabapentin, 1 h before surgery in a randomized fashion. Anesthesia was induced with propofol and cisatracurium and was maintained with sevoflurane and remifentanyl. The total intraoperative remifentanyl consumption by each patient was noted. All patients postoperatively received patient-controlled analgesia with morphine (1 mg/ml) with an incremental dose of 2 mg, a lockout interval of 10 min, and a 4-h limit of 40 mg. The incremental dose was increased to 3 mg, and the 4-h limit to 50 mg, if analgesia was inadequate after 1 h. Patients were questioned for the first 1 h in the PACU and were later evaluated in the ward at 1, 2, 4, 6, 12, and 24 h. Pain scores, heart rate, oxygen saturation measured by pulse oximetry, mean blood pressure, respiratory rate, sedation, morphine use, and total dose of morphine were recorded.

Results: Overall, pain scores at 1, 2, and 4 h were significantly lower in the gabapentin group when compared with the placebo group. Total morphine consumption in the gabapentin group was 16.3 ± 8.9 mg (mean \pm SD) versus 42.8 ± 10.9 mg in the placebo patients. The incidence of vomiting and urinary retention was significantly ($P < 0.05$) higher in the placebo group, but there was no difference in incidence of other adverse effects between the groups.

Conclusions: Preoperative oral gabapentin decreased pain scores in the early postoperative period and postoperative morphine consumption in spinal surgery patients while decreasing some morphine-associated side effects.

THE use of opioids is limited by side effects and by the poor response to opioids of certain types of pain.¹ The multiplicity of mechanisms involved in pain suggests that a combination of opioid and nonopioid analgesic drugs will enhance analgesia and reduce opioid requirements and side effects after surgery.²

Gabapentin is a structural analog of γ -aminobutyric acid, which is an anticonvulsant drug. Clinical studies

have found gabapentin to be effective in treating neuropathic pain.³ It has also been shown to be effective in diabetic neuropathy,⁴ postherpetic neuralgia,⁵ and reflex sympathetic dystrophy.⁶ In animal models of nociception, gabapentin reduces mechanical or thermal hyperalgesia⁷ and ameliorates pain associated with models of peripheral nerve injury,⁸ incisional injury,⁹ inflammatory injury,¹⁰ and formalin-induced injury.¹¹ Pretreatment with gabapentin also blocked the development of hyperalgesia.¹² Studies have demonstrated that mechanical hyperalgesia surrounding the wound in postoperative patients shares a common mechanism with (experimental) heat-induced, secondary hyperalgesia, and that central neuronal sensitization contributes to postoperative pain.¹³ The selective effect of gabapentin on the nociceptive process involving central sensitization¹² is one of the main reasons we decided to use it in the treatment of acute pain after spinal surgery in humans.

Gabapentin is a well-tolerated and safe drug.^{4,5,14} Studies have shown a synergistic effect of gabapentin with regard to the analgesic action of morphine in animal experiments¹⁵ and in humans. When used with morphine, gabapentin increased pain tolerance to cold stimulation in volunteers,¹⁶ and morphine plus gabapentin demonstrated better analgesia in patients suffering neuropathic cancer pain in comparison with morphine alone.¹⁷ In a more recent study, a single dose of oral gabapentin reduced postoperative morphine consumption and movement-related pain after radical mastectomy,¹⁸ but these results should be validated in other types of surgery before drawing a final conclusion.

The aim of the present study, therefore, was to determine the effect of gabapentin on acute postoperative pain and on morphine consumption in patients undergoing spinal surgery.

Materials and Methods

After obtaining the approval of the Institutional Ethics Committee (Trakya University, Edirne, Turkey) and the written consent of the patients, 50 patients classified as American Society of Anesthesiologists physical status I or II undergoing elective lumbar discectomy or spinal fusion surgery were studied. Patients were eligible for participation if they were at least 18 yr old, weighed more than 40 kg, and could operate a patient-controlled analgesia (PCA) device. Exclusion criteria included a known allergy, sensitivity, asthma, contraindications to morphine or any other study drug, renal insufficiency, history of peptic ulcer or of bleeding diathesis, use of narcotic analgesics or gabapentin, and pregnancy.

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The patients were randomly divided into two groups of 25. The study design was randomized and double-blinded; patients were randomly allocated according to computer-generated randomization. For premedication, 0.07 mg/kg midazolam and 0.01 mg/kg atropine were administered intramuscularly 45 min before surgery. The control group received oral placebo, and the gabapentin group received 1,200 mg gabapentin (Neurontin, 400-mg capsule; Pfizer, Goedecke GmbH, Germany), 1 h before surgery. The study drugs were prepared by the pharmacy, and an appropriate code number was assigned.

In the operating room, crystalloid infusion was started, and the mean blood pressure, heart rate, and peripheral oxygen saturation were monitored (Cato PM 8040; Dräger, Lübeck, Germany). Anesthesia was induced intravenously with 2 mg/kg propofol and 0.2 mg/kg cisatracurium and was maintained by sevoflurane with a fresh gas flow of 2 l/min (%50 air in oxygen) and remifentanyl (0.2–1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$). Remifentanyl infusion was titrated according to each patient's need; the anesthesiologist was required to maintain mean blood pressure and heart rate within $\pm 30\%$ of baseline values. Ventilation was mechanically controlled (Cato; Dräger) and adjusted to maintain end-expiratory carbon dioxide between 34 and 36 mmHg. The patients received 2 mg morphine intravenously prior to sevoflurane closure, and remifentanyl was stopped after completion of the last surgical suture. At the end of surgery, a neuromuscular block was antagonized with 1.5 mg neostigmine and 0.5 mg atropine. The total intraoperative remifentanyl consumption by each patient was noted.

After tracheal extubation, the patients were transferred to the PACU. Assessment of postoperative pain was based on the visual analog scale (0 = "no pain" and 10 = "worst pain imaginable"). Postoperative analgesia was performed with an intravenous PCA device (Abbott Pain Management Provider, North Chicago, IL). The PCA technique and the visual analog scale had been explained to the patients during the preoperative visit. The patients were connected to the PCA device on arrival at the PACU. All patients received 1 mg/ml morphine *via* the PCA with an incremental dose of 2 mg, a lockout interval of 10 min, and a 4-h limit of 40 mg. The incremental dose was increased to 3 mg, and the 4-h limit to 50 mg, if analgesia was inadequate after 1 h. Sedation was assessed by the Ramsay sedation scale. The patients were questioned during the first 1 h in the PACU and were later evaluated in the ward at 1, 2, 4, 6, 12, and 24 h. Pain scores, heart rate, oxygen saturation, mean blood pressure, respiratory rate, sedation, morphine use, and total dose of morphine were recorded by an anesthesiology resident not involved in the study. The patients were questioned about the occurrence of any adverse effects, such as nausea and vomiting, constipa-

Table 1. Duration of Surgery and Number of Patients Who Had Lumbar Discectomy or Spinal Fusion

Variable	Gabapentin (n = 25)	Placebo (n = 25)
Duration of surgery, min	156 \pm 34	160 \pm 45
Patients who had discectomy	20	19
Patients who had spinal fusion	5	6

Duration of surgery is expressed as mean + SD.

tion, respiratory depression, dizziness, somnolence, peripheral edema, diarrhea, headache, and pruritus. Morphine was stopped if the patient had a respiratory rate of less than 12 breaths per min, an oxygen saturation measured by pulse oximetry of less than 95%, or a serious adverse event related to morphine administration. On the patient's request or if nausea and vomiting occurred, 4 mg ondansetron was given intravenously.

Statistical Analysis

A sample size of 25 patients by group was calculated to detect a significant difference of 15% or more in morphine consumption with a power of 85% and a significance level of 5%. Descriptive statistics are expressed as mean \pm SD unless otherwise stated. All variables were tested for normal distribution by the Kolmogorov-Smirnov test. The Student *t* test was used for comparison of the means of continuous variables and normally distributed data; otherwise, the Mann-Whitney U test was used. Either the two-way analysis of variance or the Friedman test was used for variable differences in groups, and the Bonferroni or Tukey honest significant difference test was used for multiple comparisons. Categorical data were analyzed using the chi-square or Fisher exact test, as appropriate. Significance was determined at $P < 0.05$.

Results

From September 1, 2002, to March 15, 2003, 50 consecutive patients who fulfilled the inclusion criteria were included in the study. All 50 patients were able to complete the study; therefore, data from 50 patients were analyzed.

The groups that received either gabapentin or placebo were similar with regard to age (48 \pm 9 yr, 45 \pm 8 yr), body weight (73 \pm 15 kg, 75 \pm 13 kg), gender (male: female = 15:10, 13:12), and height (165 \pm 10 cm, 167 \pm 13 cm). The duration of surgery and number of patients who had lumbar discectomy or spinal fusion were similar (table 1). Intraoperative remifentanyl consumption (3.4 \pm 1.1 mg, 3.6 \pm 1.4 mg) was similar between the groups. The mean blood pressure, heart rate, oxygen saturation, and respiratory rate were not different between the groups in any of the measured times.

The visual analog scale scores at 1, 2, and 4 h were

Table 2. Postoperative Pain Scores in Gabapentin and Placebo Groups

Hours	Gabapentin (n = 25)	Placebo (n = 25)
1	2 (0–5)*	3 (0–6)
2	0 (0–5)*	2 (0–4)
4	0 (0–2)*	2 (0–4)
6	0 (0–2)	0 (0–4)
12	0 (0–3)	0 (0–5)
24	0 (0–2)	0 (0–3)

Pain scores are expressed as median (upper–lower quartiles in parentheses).

* $P < 0.01$, when compared with placebo group.

significantly low ($P < 0.002$, $P < 0.02$, $P < 0.000$, respectively) in the gabapentin group when compared with the placebo group (table 2). Sedation scores were similar in all of the measured times in the gabapentin or placebo groups. Morphine consumption at all of the measured times and total morphine consumption were significantly lower ($P < 0.000$) in the gabapentin group when compared with the placebo group (table 3).

The most common adverse effects observed during the study were dizziness, vomiting, and urinary retention (table 4). Incidence of vomiting and urinary retention was significantly ($P < 0.05$) higher in the placebo group; there was no difference in incidence of other adverse effects between the groups.

Discussion

The results of our preoperative, oral, single-dose study investigating the acute postoperative analgesic effects of gabapentin in spinal surgery show that gabapentin (1) decreased postoperative pain scores in the early postoperative period, (2) decreased postoperative morphine consumption throughout the study period, and (3) decreased opioid-related side effects when compared with placebo.

Gabapentin reduced tactile allodynia after incision¹⁹ and reduced mechanical hyperalgesia in a rat model of postoperative pain.⁹ Mechanical hyperalgesia surround-

Table 3. Morphine Consumptions (mg) in Gabapentin and Placebo Groups

Hours	Gabapentin (n = 25)	Placebo (n = 25)
1	4.3 ± 1.8*	6.7 ± 2.1
2	2.7 ± 1.8*	5 ± 2.4
4	2.4 ± 1.8*	6.4 ± 4.3
6	2.4 ± 2.4*	6.2 ± 3.9
12	2.9 ± 2.3*	8 ± 5.1
24	3.8 ± 4.6*	11.4 ± 5.4
Total morphine consumption	16.3 ± 8.9*	42.8 ± 10.9

Data represent interval morphine use since last measurement. Morphine doses are expressed as mean ± SD.

* $P < 0.000$, when compared with placebo group.

Table 4. Incidence of Adverse Effects Encountered through Study in Gabapentin and Placebo Groups

Variable	Gabapentin (n = 25)	Placebo (n = 25)
Dizziness	6	4
Nausea	5	7
Vomiting	1	6*
Somnolence	2	1
Diarrhea	2	1
Pruritis	1	2
Urinary retention	0	5*
Constipation	1	3

Number of patients.

* $P < 0.05$, when compared with gabapentin group.

ing the wound postoperatively and (experimental) heat-induced, secondary hyperalgesia share a common mechanism, and central neuronal sensitization might contribute to some aspects of postoperative pain. Therefore, antihyperalgesic drugs such as gabapentin may have a role in postoperative pain, and a combination of antinociceptive and antihyperalgesic drugs may provide synergistic effects.¹³

The antihyperalgesic effects of gabapentin result from an action at the $\alpha_{2\delta 1}$ subunits of voltage-dependent Ca^{2+} channels,²⁰ which are up-regulated in the dorsal root ganglia and spinal cord after peripheral injury.²¹ Gabapentin may also produce antihyperalgesia by decreasing glutaminergic transmission in the spinal cord.²² In addition, gabapentin may inhibit central sensitization and its behavioral correlate of thermal hyperalgesia through an action at voltage-dependent Ca^{2+} channels resulting in a direct postsynaptic inhibition of Ca^{2+} influx or a presynaptic inhibition of Ca^{2+} influx that decreases excitatory amino acid neurotransmission and its sequelae.²³

Gabapentin enhanced the analgesic effect of morphine in healthy volunteers¹⁶ and, combined with morphine in patients with neuropathic cancer pain, demonstrated better analgesia in comparison with morphine alone.¹⁷ In a recent study,¹⁸ gabapentin significantly decreased morphine consumption and pain in patients after mastectomy, although they were evaluated for only 4 h. In our study, we demonstrated a similar reduction in pain in the first 4 h; however, morphine consumption was reduced throughout the 24-h period. Side effects were similar in the study by Dirks *et al.*¹⁸; however, we determined a decrease in side effects associated with opioid consumption, demonstrating that a multimodal analgesic approach using adjunctive drugs reduces the need for opioid analgesics and decreases side effects. In a study investigating the effect of 1,200 mg gabapentin after breast surgery, a 50% reduction in analgesic requirements was observed during the first postoperative week; however, the study did not further demonstrate a decrease in analgesic requirements during the first 24 h.²⁴ Our results are contrary with these results, possibly because of the different types of surgery, opioids, and

pain protocols. Further studies are needed to determine the effect of gabapentin in different postoperative pain models.

Gabapentin is well tolerated and has few side effects and minor interactions with other drugs. Studies on safety issues^{12,25} have demonstrated the following adverse effects: dizziness, somnolence, confusion, headache, nausea, ataxia, and weight gain. However, these studies were usually performed in patients with long-term gabapentin use. In our study, we used only a single oral dose and observed no significant adverse effects associated with gabapentin. An important limitation of our study is the lack of examination of more than one dose; future investigations for determining dose-response relation will be required.

In conclusion, gabapentin decreased pain scores in the early postoperative period and decreased postoperative morphine consumption while decreasing the side effects associated with morphine in patients undergoing spinal surgery. Further studies are required in different pain models to investigate the efficacy and safety of gabapentin alone or in combination with other analgesics.

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