Effect of oral gabapentin on postoperative epidural analgesia

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Background. Gabapentin has been used successfully as a non-opioid analgesic adjuvant for postoperative pain management. We hypothesized that gabapentin might be a useful adjuvant for postoperative analgesia provided with patient-controlled epidural analgesia (PCEA).

Methods. Forty patients undergoing lower extremity surgery procedures were randomly assigned to receive (i) placebo capsules (control) or (ii) gabapentin (1.2 g day\(^{-1}\)) before and for 2 days after surgery. Anaesthetic technique was standardized. Postoperative assessments included verbal rating scale scoring for pain and sedation, PCEA usage, quality of recovery assessment, times of GI function recovery, and patient satisfaction scoring for pain management.

Results. Pain scores at 1, 4, 8, 12, and 16 h (\(P<0.001\)), PCEA bolus requirements (n) at 24 [21 (3), 14 (2)], 48 [15 (4), 10 (3)] and 72 [8 (5), 2 (3)] (\(P<0.05\)) and paracetamol (mg) consumption [700 (523), 350 (400)] (\(P<0.05\)), were significantly lower in the gabapentin-treated patients than in the control group. Patient satisfaction with postoperative pain management at 24 h was better in gabapentin-treated patients [85.5 (7.5), 66.5 (15)] (\(P<0.001\)). Gabapentin-treated patients had less motor block when compared with control group. Times of return of bowel function, hospitalization, and resumption of dietary intake were similar in the groups. However, the incidence of dizziness was higher in the gabapentin group (35% vs 5%; \(P<0.05\)).

Conclusions. Oral gabapentin (1.2 g day\(^{-1}\)) as an adjunct to epidural analgesia decreased pain and analgesic consumption. Despite an increased incidence of dizziness it also increased patient satisfaction.

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Postoperative pain slows recovery from anaesthesia and surgery. Many types of analgesics have been used alone or in combination for its treatment. Postoperative pain is typically regarded as a type of nociceptive pain involving peripheral mechanoreceptor stimulation, inflammatory, and neurogenic and visceral mechanisms, with a transient, reversible type of neuropathic pain.\(^1\) Surgical stimulation leads to sensitization of dorsal horn neurones, which are associated with augmentation of pain. Regional analgesia, especially epidural local anaesthetics and opioids, are frequently used for the treatment of postoperative pain in lower abdominal or extremity surgery.

Gabapentin, an anticonvulsant drug, was first reported to be effective for the treatment of neuropathic pain\(^2\) and diabetic neuropathy.\(^3\) It has also been shown to reduce postoperative pain and opioid analgesic requirements in a variety of acute postoperative pain models.\(^4-8\) Intrathecal gabapentin significantly enhances the effect of an intrathecal, sub-analgesic dose of morphine in the rat.\(^9\) Additionally, combined spinal administration of gabapentin and low doses of morphine significantly reduced pain-related behaviour in an acute rat pancreatitis model. These agents were ineffective when used alone in the selected dose ranges.\(^10\) Such data suggest that the \(\alpha_2\delta_1\) subunit of the N-type voltage-activated Ca\(^{2+}\) channels is involved in transmission of this visceral pain, probably through effects on primary afferent endings in the spinal cord. Thus,
Gabapentin may be an effective adjuvant to initial low dose spinal opioid therapy for clinical management of visceral pain.

With this background, we designed this study to test the hypothesis that the perioperative use of oral gabapentin will reduce consumption of epidural analgesics after lower extremity surgery. Our secondary objectives were to determine whether supplementing epidural analgesia with gabapentin can also alter postoperative pain scores, recovery times, side-effects, resumption of normal activities, and patient satisfaction.

Materials and methods

After approval by the Institutional Ethics Committee (Trakya University, Edirne, Turkey) and written informed consent, 40 patients undergoing elective lower limb surgery were enrolled in this study. Patients were eligible for enrollment if they were >18 yr old, within ±50% of their ideal body weight, had no clinically significant cardiovascular or central nervous system diseases, and could operate a patient-controlled analgesia (PCA) device. Exclusion criteria were known allergy to any of the study medications; contraindications to the use of PCA, bupivacaine, or any anaesthetic drugs, renal insufficiency, peptic ulcer disease, and history of bleeding diathesis or drug abuse.

The patients were randomly assigned to one of two treatment groups using a computer-generated table. Patients in the control group received oral placebo capsules and the study group patients received oral gabapentin 1.2 g (Neurontin™, Pfizer, Goedecke GmbH, Germany) 1 h before surgery. The same drugs were administered at 09:00 on the first and second postoperative days. The gelatin encapsulated capsules were prepared by the pharmacy in order to maintain double-blind conditions, and an appropriate code number was assigned to each patient.

All patients received premedication with midazolam, 0.07 mg kg⁻¹ i.m., 45 min before surgery. Upon arrival in the operating room, a crystalloid i.v. infusion 6–8 ml kg⁻¹ h⁻¹ was started in all patients, and baseline mean arterial pressure, heart rate, and peripheral oxygen saturation readings were obtained (Cato PM 8040, Dräger, Lübeck, Germany). Anaesthesia was induced with propofol (2 mg kg⁻¹) and atracurium (0.5 mg kg⁻¹), and was initially maintained with sevoflurane 2% at a fresh gas flow rate of 2 litre min⁻¹ in combination with nitrous oxide 50% in oxygen. Fentanyl, 2 μg kg⁻¹ i.v., was administered 3–5 min before the surgical incision. A 16-gauge Tuohy needle was used to insert an epidural catheter at the L2–3 or L3–4 interspace (patients specifically requested to have this done under anaesthesia with full knowledge and consent that this might be associated with an increased risk for neurological injury). In all patients, a midline approach was used with the epidural space identified using loss of resistance to saline. If there was no blood or cerebrospinal fluid aspiration and no abnormal reaction after an epidural test dose with 1:200 000 epinephrine, the catheter was secured and surgery commenced. All patients received mechanical ventilation to maintain the end-expiratory carbon dioxide between 4.5 and 4.8 kPa. Hypotension (MAP >25% below baseline for at least 60 s) was treated with ephedrine 5–10 mg i.v., bradycardia (heart rate<50 bpm) was treated with atropine 20 μg kg⁻¹ i.v., and incidence recorded. Intraoperative blood loss was replaced with crystalloid fluids at a 3:1 ratio or allogeneic blood transfusions at a 1:1 ratio as clinically required. An epidural loading dose of bupivacaine 0.125% 5 ml, with fentanyl 1 μg ml⁻¹, was administered 30 min before discontinuing sevoflurane and nitrous oxide.

At the start of skin closure, residual neuromuscular block was antagonized with neostigmine, 1.5 mg and atropine, 0.5 mg i.v. One research resident collected data during the perioperative period, and two research residents collected the data after operation, all were blinded to group assignment.

After tracheal extubation and awakening from anaesthesia, patients were transferred to the post anaesthesia care unit (PACU). Assessment of postoperative pain was with an 11-point verbal rating scale (VRS), with 0=‘no pain’ and 10=‘worst pain imaginable’. Patients were then connected to an epidural PCA device and postoperative analgesia was provided with an epidural PCA solution containing bupivacaine 0.125% and fentanyl 1 μg ml⁻¹, with a bolus dose set at 5 ml, lockout interval of 10 min and a 4 h limit of 40 ml. The bolus was increased to 8 ml if analgesia was inadequate after 1 h of PCA use.

Sedation was assessed using an 11-point VRS, with 0=no sleepiness or drowsiness to 10=almost aslepp or extremely drowsy. Assessments of pain, sedation, the degree of motor blockade evaluated by Bromage scale (1=no motor block, 2=knee blocked and mobility of ankle preserved, 3=mobility of ankle difficult, and 4=knee and ankle blocked), analgesic usage, and side-effects were performed at 1, 4, 8, 12, 16, 20, 24, 30, 36, 42, 48, 60, and 72 h after arrival in the PACU. The PCA device was discontinued when the patient made no demands in the preceding 4 h interval. Oral analgesia was then provided with paracetamol on demand, 500 mg PO every 6–8 h.

Postoperative side-effects (e.g. nausea and vomiting, constipation, respiratory depression, dizziness, somnolence, peripheral oedema, diarrhoea, headache and pruritus) were recorded at 24, 48, and 72 h after surgery. Patients with a nausea score of ≥4 (assessment of postoperative nausea was performed using an 11-point VRS, with 0=no nausea and 10=worst nausea imaginable) and those who vomited or requested antiemetics, received ondansetron 4 mg i.v.

The patients were asked to note the time they first passed flatus and first moved their bowels after surgery. In addition, when the research assistants assessed their pain, they also asked whether the patient had had flatus or a bowel movement. Twice daily, the surgeon auscultated the abdomen for bowel sounds and documented the presence or absence of bowel sounds in the patient’s chart. Resumption of oral
dietary intake and ambulation were evaluated at regular intervals (every 2 h) during the day by the blinded research assistant.

Patient satisfaction with their postoperative analgesia was assessed using a 101-point VRS, with 0 being highly dissatisfied to 100 completely satisfied. A research assistant blinded to the study medication recorded all measurements. Before being discharged from the hospital, all patients were asked to assess their quality of recovery using a standardized questionnaire.11

Statistical analysis

Based on a preliminary study [epidural use of 20 (2.2) boluses, mean (SD)], a sample size of 20 patients per group was calculated to detect a significant difference of 10% or more in epidural analgesic consumption with a power of 80% and a significance level of 5%. Descriptive statistics are expressed as mean (SD) unless otherwise stated. All variables were tested for normal distribution by Kolmogorov–Smirnov test. Student’s t-test was used for comparison of the means of continuous variables and normally distributed data. Mann–Whitney U-test was used otherwise. Two-way analysis of variance (ANOVA) or Friedman tests were used for variable differences in groups, and Bonferroni or Tukey HSD tests were used for multiple comparisons. Categorical data were analysed using χ²-test analysis or the Fisher Exact test, as appropriate. Statistical significance was defined as P<0.05.

Results

Between October 1, 2003 and January 1, 2005, a total of 54 patients were assessed for study eligibility (four patients failed to meet the inclusion criteria and five patients refused participation). The remaining 45 patients who fulfilled the entry criteria were enrolled in this study. Five patients were excluded because of study violations. The remaining 40 patients were able to complete the study and their data were included in the final analysis. The groups were comparable with respect to age, body weight, height, ASA physical status, and duration of surgery (Table 1). The mean blood pressure, heart rate, oxygen saturation, and ventilatory frequency did not differ between the groups at any of the measured time intervals (data not reported). Sedation scores were also similar between the groups at all the measured time intervals.

The VRS pain scores were significantly greater at 1, 4, 8, 12, and 16 h after operation in patients receiving placebo than in those receiving gabapentin (P<0.001) (Fig. 1). Analysis of the AUC for the pain scores showed a statistically significant difference for the first 24 h (P<0.001) but not at 72 h (P=0.703). ANOVA for repeated measures confirmed that gabapentin reduced postoperative pain scores (F=14.4, P=0.01).

Compared with the placebo group, PCEA requirements were significantly reduced in the gabapentin-treatment group at 24, 48, and 72 h after surgery (Table 2). In addition, oral analgesic consumption was less in the

![Pain score over time](image)
Gabapentin and epidural analgesia

Table 4 Patient satisfaction with pain management, occurrence of postoperative side-effects, and need for antiemetic therapy. Values are expressed as mean (SD) or number. VRS, verbal rating scale; 1, not satisfied at all, 100, totally satisfied. *P<0.05 compared with placebo group. **P<0.001 compared with placebo group.

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=20)</th>
<th>Gabapentin (n=20)</th>
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<tr>
<td>Patient satisfaction (1–100 VRS score)</td>
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</tr>
<tr>
<td>At 24 h</td>
<td>66.5 (15)</td>
<td>85.5 (7.5)**</td>
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<tr>
<td>At 48 h</td>
<td>77.4 (8)</td>
<td>90 (5.2)**</td>
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<tr>
<td>At 72 h</td>
<td>87.1 (8.5)</td>
<td>97.2 (4.1)*</td>
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<td>Postoperative side-effects (n)</td>
<td></td>
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<tr>
<td>Hallucinations</td>
<td>0</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (5%)</td>
<td>7 (35%)*</td>
</tr>
<tr>
<td>Nausea</td>
<td>14 (70%)</td>
<td>10 (50%)</td>
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<tr>
<td>Vomiting</td>
<td>10 (50%)</td>
<td>9 (45%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (10%)</td>
<td>5 (25%)</td>
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<tr>
<td>Diarrhoea</td>
<td>1 (5%)</td>
<td>2 (10%)</td>
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<tr>
<td>Pruritis</td>
<td>1 (5%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Urinary retention</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4 (20%)</td>
<td>4 (20%)</td>
</tr>
<tr>
<td>Antiemetic usage (n)</td>
<td>13 (65%)</td>
<td>9 (45%)</td>
</tr>
</tbody>
</table>

 gabapentin-treated patients compared with the control group (Table 3). However, the groups were similar in times to the return of bowel function, resumption of dietary intake, and length of hospitalization. Fewer of the gabapentin-treated patients had motor block (Bromage scale scores of 0 (5;13), 1 (2;0), 2 (5;2), 3 (5;3), or 4 (3;2) for gabapentin- and placebo-treated groups, respectively) (P<0.05).

Patient satisfaction with their postoperative pain management was significantly greater at 24, 48, and 72 h in the gabapentin group compared with the control group (Table 3).

The most common side-effects during the postoperative period were nausea, vomiting, and dizziness (Table 4). The incidence of dizziness was greater in the gabapentin group than in the control group.

Discussion

Our study shows that, in lower extremity surgery, gabapentin decreased postoperative pain scores in the early postoperative period, decreased postoperative epidural analgesic consumption throughout the study period, and had a higher satisfaction score than the control group.

Pain signals from the nociceptors may result in sensitization of secondary nociceptive neurones in the dorsal horn. This is mediated by a decrease in inhibitory input or an increase in synaptic efficacy or membrane excitability triggered by wind-up neurokinin and N-methyl-D-aspartic acid (NMDA) receptor mechanisms.12 13 Subsequently, activity in nociceptors and non-nociceptive A-beta fibres will be amplified, which leads to increased pain, hyperalgesia, and allodynia.1

A possible mechanism for gabapentin-mediated analgesia is the modulation of glutamate receptors (NMDA and AMPA/kainate). Gabapentin seems to decrease both NMDA and non-NMDA-mediated glutamate currents in the superficial lamina of the rat spinal cord14 and also inhibits nociceptive responses to intrathecal NMDA and AMPA in vivo.15 Furthermore, the analgesic effects of gabapentin are antagonized by the NMDA/glycine receptor agonist serine.16 17 Suarez and colleagues18 suggest that sodium entry through presynaptic NMDA-R channels facilitates axon excitability and the interaction of gabapentin with this mechanism might contribute to its analgesic benefits. Gabapentin has no direct GABA action and does not block GABA uptake or metabolism.19 Another suggested mechanism for gabapentin is that it binds to the voltage-dependent calcium channels.20 All, or any, of the suggested mechanisms may be responsible for the analgesic action of gabapentin.

Recent studies suggest that gabapentin may be useful in the perioperative setting, as an adjuvant to parenteral opioid analgesics in the postoperative period.14 – 7 Our study shows a different usage, as the first clinical study using gabapentin as an adjuvant to regional analgesia. The main aim of combining different analgesic drugs and techniques is to obtain synergistic or additive actions that allow a smaller dose of each agent to be used and, thereby, improve the safety profile. This can be achieved by combining analgesics acting at different locations, for example, centrally and peripherally acting analgesics.

A limitation of the current study design is that we did not have dose–response data before choosing the dose used in the study. However, by choosing the highest reasonable dose, we avoided the risk of a considerably larger study with a potentially negative outcome. Patients in the control group reported unacceptably high pain VAS scores in the early postoperative period. This finding was unexpected as we used the standard analgesic regimen established in our department and patients do not usually complain of unacceptable pain. We have, therefore, subsequently increased the standard analgesic loading dose. However, these high pain levels in the control group supported the efficacy of gabapentin. Another limitation might be that gabapentin was given as a single dose, which may have resulted with a decreased effect over time. The half-life of gabapentin is 5–7 h and further studies with divided doses are needed.

In summary, oral gabapentin, 1200 mg day−1, decreased the dose requirement of epidural analgesia and postoperative pain. In addition, patients receiving gabapentin were more satisfied with their pain control than those receiving placebo. We believe that, as a part of multimodal analgesia, gabapentin is a useful adjuvant to epidural analgesia after lower extremity surgery.

Acknowledgement

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