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A Randomized Study of the Effects of Single-dose Gabapentin versus *Placebo on Postoperative Pain and Morphine Consumption after Mastectomy*

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Background: **The anticonvulsant gabapentin has proven effective for neuropathic pain in three large placebo-controlled clinical trials. Experimental and clinical studies have demonstrated antihyperalgesic effects in models involving central neuronal sensitization. It has been suggested that central neuronal sensitization may play an important role in postoperative pain. The aim of the study was to investigate the effect of gabapentin on morphine consumption and postoperative pain in patients undergoing radical mastectomy.**

Methods: **In a randomized, double-blind, placebo-controlled study, 70 patients received a single dose of oral gabapentin (1,200 mg) or placebo 1 h before surgery. Patients received patient-controlled analgesia with morphine at doses of 2.5 mg with a lock-out time of 10 min for 4 h postoperatively. Pain was assessed on a visual analog scale at rest and during movement, and side effects were assessed on a four-point verbal scale 2 and 4 h postoperatively.**

Results: **Thirty-one patients in the gabapentin group and 34 patients in the placebo group completed the study. Gabapentin reduced total morphine consumption from a median of 29 (interquartile range, 21–33) to 15 (10–19) mg ($P < 0.0001$). Pain during movement was reduced from 41 (31–59) to 22 (10–38) mm at 2 h postoperatively ($P < 0.0001$) and from 31 (12–40) to 9 (3–34) mm at 4 h postoperatively ($P = 0.018$). No significant differences between groups were observed with regard to pain at rest or side effects.**

Conclusion: **A single dose of 1,200 mg oral gabapentin resulted in a substantial reduction in postoperative morphine consumption and movement-related pain after radical mastectomy, without significant side effects. These promising results should be validated in other acute pain models involving central neuronal sensitization.**

THE anticonvulsant gabapentin is widely used for treatment of chronic pain and has reduced neuropathic pain in three large placebo-controlled clinical trials.[1–3] Despite intensive investigation, the molecular mechanism of action of gabapentin remains unsettled (for review, see Taylor *et al.*[4]). Experimental studies have demonstrated antihyperalgesic effects of gabapentin in models involving central neuronal sensitization, without affecting acute pain transmission.[5] In healthy volunteers, gabapentin enhanced the effect of morphine in the cold pressor test,[6] reduced primary mechanical allodynia in acute inflammation following a thermal injury,[7] and reduced secondary hyperalgesia following sensitization with combined heat and capsaicin, without affecting acute nociceptive thresholds.[8]

It has been suggested that central neuronal sensitization may amplify postoperative pain, although the relative contribution of various pain mechanisms to postoperative pain has not been established.[9] The hypothesis of the present study was that gabapentin, due to its potent antihyperalgesic effects, may reduce postoperative pain.

The objective of the study was therefore to investigate the effect of a single dose of 1,200 mg oral gabapentin on morphine consumption and pain in the immediate postoperative period after unilateral radical mastectomy and axillary dissection. The design and description of the present trial adhere to the Consolidated Standards of Reporting Clinical Trials statement.[10]

Materials and Methods

Participants

Women aged 18–75 yr who were scheduled for unilateral radical mastectomy with axillary dissection were eligible for the study. Patients were not included if they were unable to cooperate, had known allergy to gabapentin or morphine, a history of drug or alcohol abuse, chronic pain or daily intake of analgesics or corticosteroids, diabetes, or impaired kidney function. Patients with an intake of NSAIDs or paracetamol 24 h prior to operation or an intake of antacids 48 h prior to operation were also excluded from the study. Patients were recruited from the Department of Breast Surgery, Herlev University Hospital (Herlev, Denmark), during the period December 2000 to October 2001.

Written informed consent was obtained from all patients, and the study was approved by the Regional Ethics Committee (Herlev, Denmark) and The Danish National Health Board (Copenhagen, Denmark).

Interventions

Patients received 0.125 mg sublingual triazolam and 1,200 mg oral gabapentin or placebo 1 h before surgery.

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General anesthesia was induced with 1.5–2.5 mg/kg propofol, and infusion of 1 μg/kg remifentanil for 1 min. A laryngeal mask was inserted. Anesthesia was maintained with infusion of propofol at the discretion of the anesthetist, and a fixed infusion of 0.4 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil. Hypotension was treated with isotonic sodium chloride, 6% hetastarch in saline, and/or 5 mg ephedrine intravenously in incremental doses, in order to preserve systolic blood pressure above 90 mmHg.

The infusions of propofol and remifentanil were terminated at skin closure; 0.5 mg alfentanil was administered intravenously to all patients, who were then transferred to the postoperative care unit. Postoperative pain treatment consisted of patient-controlled intravenous morphine (Abbott Pain Management Provider; Abbott, Virum, Denmark), 2.5-mg bolus, 10 min lock-out time. Additional morphine, 2.5 mg intravenously, was administered by a nurse observer, if requested by the patient, during the lock-out period. Ondansetron, 4 mg intravenously, was administered on patient request. No other medications were administered during the 4-h observation period.

Outcomes and Assessments

The primary outcome measure was total morphine consumption from 0 to 4 h postoperatively. Secondary outcome measures were pain at rest and during mobilization from the supine to the sitting position, and side effects: nausea, somnolence, lightheadedness, dizziness, headache, visual disturbances, and vomiting.

Before surgery, all patients were instructed in the use of patient-controlled analgesia and the visual analog scale (0 mm = no pain, 100 mm = worst pain imaginable). To ensure equal assessment methods, all assessors were instructed carefully by the primary investigator (J. Dirks) before participating in the study.

Total morphine consumption was recorded from 0 to 4 h postoperatively. Pain scores (visual analog scale) at rest and during mobilization were assessed by the patients at 2 and 4 h after surgery.

Side effects were rated on a four-point verbal scale (none, mild, moderate, severe) at 2 and 4 h after surgery. The number of patients vomiting, as well as use of antiemetics, was recorded.

Study Population Size

Based on preliminary results from our department, the anticipated morphine requirement was 25 mg/4 h (SD = 10). We considered a 30% reduction in morphine consumption to be clinical relevant. With a type 1 error of 5% and a power of 90%, 32 patients were required in each study group.

Blinding

The study was randomized, double-blind, and placebo-controlled. Study medication was prepared by the hospital pharmacy into identical capsules containing either 300 mg gabapentin, or placebo. Study medication was marked with the name of the project, the investigator's name, and consecutive numbers according to a computer-generated block randomization schedule prepared by the hospital pharmacy. Patients were enrolled by the same investigators who also performed the assessments. Participants were assigned consecutively to their group according to their number. No person was aware of group assignment until all 70 patients had been included and assessments were completed.

Statistical Methods

Data are presented as medians with lower and upper quartiles. Variables were evaluated with the Mann–Whitney rank sum test for unpaired data. All significant *P* values were corrected with the Bonferroni test for repeated measurements. $P < 0.05$ was considered statistically significant. Calculations were performed using SPSS 10.0 for Windows (SPPS, Chicago, IL). The statistical analysis was performed by the investigators.

Results

From December 6, 2000 to October 5, 2001, 87 consecutive patients who fulfilled the inclusion criterions were considered for inclusion in the study (fig. 1). Seventeen patients were not included: six patients did not want to participate; eight patients were not included due to lack of time of the investigators; one patient had paracetamol the morning before surgery; one patient claimed that she was not able to swallow the study medication; one patient had breast implants, which should be removed before mastectomy.

Seventy patients were included in the study; however, five of these were subsequently excluded, four in the gabapentin and one in the placebo group. In the gabapentin group, one patient was unable to swallow the study medication, one patient was reoperated due to bleeding 3 h after the primary operation, one patient received medication other than prescribed in the study protocol, and one patient was not connected properly to the patient-controlled analgesia device. In the placebo group, one patient was excluded due to incorrect connection to the patient-controlled analgesia device. Thus, data from 65 patients, 31 of 35 in the gabapentin group and 34 of 35 in the placebo group, were included and analyzed.

Baseline demographic and clinical characteristics of each group appear in table 1. No significant differences were observed between groups.

Morphine Consumption

Total morphine consumption was reduced from 29 (21–23) mg in the placebo group to 15 (10–19) mg in the gabapentin group ($P < 0.0001$).

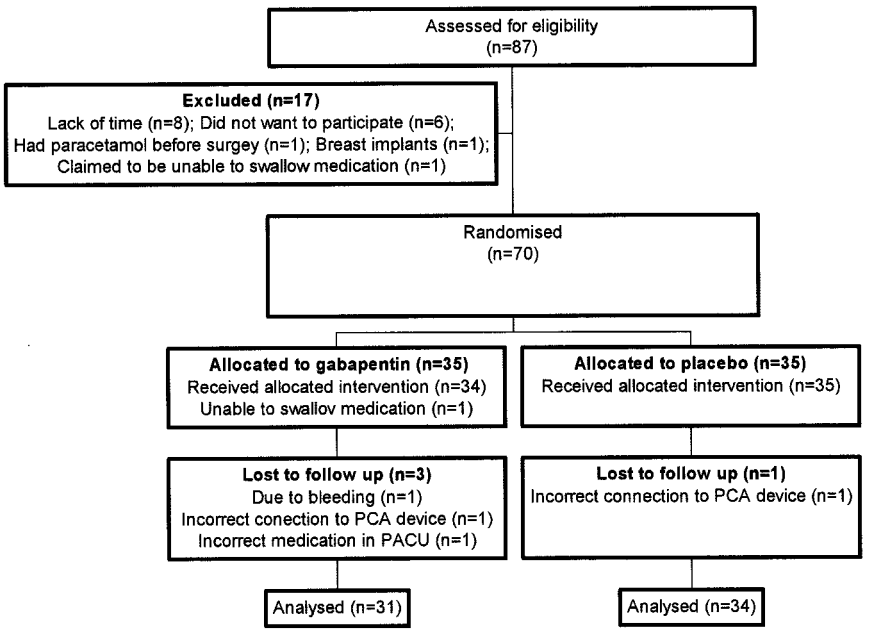

Fig. 1. Flow diagram of patient distribution.

Pain Scores

Pain at rest was reduced from 33 (23–44) mm in the placebo group to 19 (10–43) mm in the gabapentin group at 2 h postoperatively, and from 12 (9–30) to 7 (1–18) mm at 4 h postoperatively. These reductions were not statistically significant ($P = 0.094$ and $P = 0.084$, respectively, after Bonferroni correction; fig. 2A). Pain during movement was reduced from 41 (31–59) mm in the placebo group to 22 (10–38) mm in the gabapentin group at 2 h postoperatively ($P < 0.0001$), and from 31 (12–40) to 9 (3–34) mm at 4 h postoperatively ($P = 0.018$, after Bonferroni correction; fig. 2B).

Side Effects

The incidence of side effects appears in table 2. The most common side effect was somnolence, which was typically described as mild to moderate. Lightheadedness and dizziness were also common and were also described as mild to moderate, whereas other adverse effects were rare. No significant differences were observed in any outcome between groups ($P > 0.05$ for all observations; table 2). One patient in each group vomited; eight patients in the gabapentin group and five patients in the placebo group received ondansetron ($P > 0.05$).

Table 1. Demographics

	Placebo	Gabapentin
No. of patients (n)	34	31
Age (yr)	60 (52–69)	61 (54–67)
Height (cm)	167 (165–171)	164 (160–173)
Weight (kg)	73 (60–84)	70 (57–86)
Duration of surgery (min)	120 (107–135)	122 (96–149)
Perioperative propofol (mg)	1023 (897–1206)	925 (686–1141)
Perioperative remifentanil (mg)	4.2 (3.3–5.1)	3.9 (2.7–5.2)

Patient and perioperative data (median, lower and upper quartiles). No significant differences between groups.

Discussion

A single dose of 1,200 mg oral gabapentin administered preoperatively resulted in a 50% reduction in postoperative morphine consumption and in a substantial reduction in movement-related pain 2 and 4 h after radical mastectomy. Pain at rest was also reduced by gabapentin, but this reduction was not statistically sig-

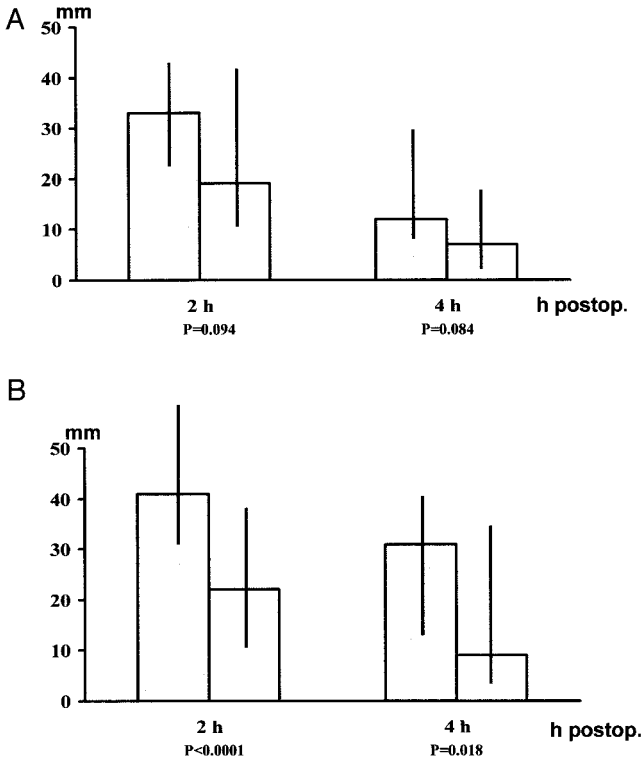

Fig. 2. Visual analog scale score during rest (*A*) and mobilization (*B*) after treatment with placebo (gray) or gabapentin (white) at 2 and 4 h postoperatively (median, lower and upper quartiles).

Table 2. Side Effects

Side Effect	2 h Postoperatively		4 h Postoperatively	
	Placebo (N = 34)	Gabapentin (N = 31)	Placebo (N = 34)	Gabapentin (N = 31)
Nausea				
Mild	2	2	1	2
Moderate	—	—	2	—
Severe	1	—	—	—
Somnolence				
Mild	14	11	15	11
Moderate	10	8	7	5
Severe	3	4	—	4
Lightheadedness				
Mild	10	12	12	8
Moderate	7	6	3	6
Severe	—	2	1	2
Dizziness				
Mild	6	5	9	7
Moderate	3	4	2	1
Severe	—	—	—	—
Headache				
Mild	1	—	1	—
Moderate	1	1	—	1
Severe	—	—	—	—
Visual disturbances				
Mild	—	—	—	—
Moderate	2	3	3	2
Severe	1	1	1	—

Number of patients experiencing side effects at 2 and 4 h postoperatively in the placebo and gabapentin groups. No significant differences between groups.

nificant. No significant differences in side effects were observed between gabapentin and placebo in this study, with patients evaluated in the first 4 h after a general anesthetic.

Gabapentin has demonstrated potent antihyperalgesic properties in preclinical and clinical studies, without affecting acute nociception.[5,8] In experimental studies, gabapentin suppressed experimentally induced hyperalgesia.[11–13] Intrathecal administration reduced tactile allodynia after incision,[14] enhanced pain behavior in rats after formalin induced pain,[15] and reduced mechanical hyperalgesia in a rat model of postoperative pain.[16] In a recent clinical study, gabapentin demonstrated a substantial inhibitory effect not only on the development of but also on established secondary allodynia and hyperalgesia resulting from sensitization of the skin with heat and capsaicin in volunteers.[8] The magnitude of this effect was comparable with the effect observed with the potent opioid remifentanil in another study,[17] but in contrast, without affecting acute nociceptive thresholds[8] and with only moderate side effects. The observed selective effect on allodynia and hyperalgesia[8] is comparable with results with ketamine, but without the psychomimetic side effects observed with this NMDA receptor antagonist.[18]

It has been suggested that central neuronal sensitization may play an important role not only in chronic pain states such as neuropathic pain, but also in postoperative pain.[9] The relative contribution of various pain mechanisms to postoperative pain has, however, not been established. A number of "antihyperalgesic" methods and drugs, including "preemptive analgesia"[19] and NMDA receptor antagonists,[20–22] have been evaluated in order to reduce the central neuronal hyperexcitability, which theoretically may amplify postoperative pain. Results, however, have been discordant and not clinically impressive.

So far, the potential effect of gabapentin on acute, postoperative pain has not been evaluated in clinical studies. Pregabalin is an analog of the inhibitory neurotransmitter γ-aminobutyric acid. In a randomized, double-blind, placebo-controlled, parallel-group trial, 300 mg pregabalin was compared to placebo and 400 mg ibuprofen using a dental pain model.[23] Results showed that there were statistically significant differences in pain relief, pain intensity difference, and pain relief intensity difference between the 300-mg pregabalin group and placebo. Consequently, pregabalin appears to have significant analgesic properties in the third molar extraction model.

The mechanism of action of gabapentin in the present study could be explained by prevention or reduction of the development of central neuronal hyperexcitability induced by the surgical procedure. This hypothesis is further supported by the fact that only evoked pain during movement that is during augmented afferent transmission to dorsal horn neurons was significantly decreased, in contrast to pain at rest, where effects were less definite and not statistically significant. It should be noted, though, that pain at rest in the placebo group was only modest, especially at 4 h postoperatively, which makes it difficult to demonstrate an analgesic effect of any intervention.

Another explanation to the observed effects of gabapentin may be that intraoperative remifentanil increased postoperative pain and morphine requirement due to induction of acute opioid tolerance[24] and that gabapentin may modulate this tolerance, as observed with NMDA receptor antagonists.[25] In a recent study, however, no clinical evidence of induction of acute opioid tolerance after remifentanil-based anesthesia was observed,[26] and this explanation remains speculative.

No significant differences in side effects were observed between placebo and gabapentin in the present study, despite the fact that a rather large dose of gabapentin was administered. It should be noted that patients were assessed in the immediate postoperative period, from 0 to 4 h after surgery and a general anesthetic, and that this may have masked side effects due to gabapentin. Furthermore, our study was not powered to investigate side effects of gabapentin *per se*. Dizziness and somnolence have been demonstrated to be the most common adverse events of gabapentin in previous controlled studies of chronic pain.[1–3] The situation in the

postoperative period is quite different from that of chronic pain states, however, and gabapentin may have a favorable side effect profile in the postoperative period, compared with, for example, opioids.

In conclusion, this is the first clinical study to demonstrate an analgesic or antihyperalgesic effect of gabapentin in somatic, postoperative pain. These promising results should be validated in other surgical procedures, with multiple dosing and prolonged follow-up. In addition to its potential effects on postoperative pain, gabapentin and analogs may prove valuable as tools in the study of acute pain mechanisms.[27]

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