

Preoperative Gabapentin Decreases Anxiety and Improves Early Functional Recovery from Knee Surgery

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Gabapentin has antihyperalgesic and anxiolytic properties. We thus tested the hypothesis that premedication with gabapentin would decrease preoperative anxiety and improve postoperative analgesia and early postoperative knee mobilization in patients undergoing arthroscopic anterior cruciate ligament repair under general anesthesia. Forty patients were randomly assigned to receive 1200 mg oral gabapentin or placebo 1–2 h before surgery; anesthesia was standardized. Patients received morphine, 0.1 mg/kg, 30 min before the end of surgery and postoperatively via a patient-controlled pump. Pain scores and morphine consumption were recorded over 48 h. Degrees of active and passive knee flexion and extension were recorded during physiotherapy on days 1 and 2. Preoperative anxiety

scores were less in the gabapentin than control group (visual analog scale scores of 28 ± 16 mm versus 66 ± 15 mm, respectively; $P < 0.001$). The gabapentin group required less morphine than the control group (29 ± 22 mg versus 69 ± 40 mg, respectively; $P < 0.001$). Visual analog scale pain scores at rest and after mobilization were significantly reduced in the gabapentin group. First and maximal passive and active knee flexions at 24 and 48 h were significantly more extensive in the gabapentin than in the control group. In conclusion, premedication with 1200 mg gabapentin improved preoperative anxiolysis, postoperative analgesia, and early knee mobilization after arthroscopic anterior cruciate ligament repair.

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Various nociceptive mechanisms are involved in postoperative pain, including sensitization of peripheral nociceptive nerve terminals and central neurons. In particular, central neuronal sensitization apparently contributes to postoperative pain hypersensitivity (1), which is characterized by an area of mechanical hyperalgesia in undamaged skin surrounding the surgical wound (2). More recent findings support the hypothesis that this mechanical sensitivity adjacent to the injured area in postoperative patients is similar in its mechanism to heat-induced secondary hyperalgesia, sharing a common mechanism with it (i.e., central neuronal sensitization) (3).

Central neuronal sensitization probably contributes to some aspects of postoperative pain; thus, Woolf and

Chong (1) suggested using antihyperalgesic drugs to improve postoperative pain treatment. Antihyperalgesic drugs, by preventing the development of central excitability, also elicit analgesic effects that extend beyond their pharmacological actions. Such preventive analgesia is well documented in response to administration of *N*-methyl-D-aspartate (NMDA) receptor antagonists such as ketamine and dextromethorphan (4).

Gabapentin is effective for neuropathic pain, diabetic neuropathy, postherpetic neuralgia, and reflex sympathetic dystrophy (5). It is an antihyperalgesic drug that selectively affects the nociceptive process involving central sensitization (5). In volunteers, oral gabapentin profoundly suppressed established cutaneous hyperalgesia after heat-capsaicin sensitization and was able to prevent the development of cutaneous sensitization (6). Moreover, gabapentin is relatively well tolerated and belongs to a class of drugs that have anxiolytic properties (7). Each of these properties suggests that gabapentin may be useful preoperatively.

The use of gabapentin in the perioperative setting has been evaluated in recent studies (8–13). These studies report promising reductions in postoperative morphine consumption (8–12) and movement-related pain (8,9,12). However, these studies did not involve

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patients undergoing joint surgery. They were therefore unable to evaluate the potential of gabapentin to improve postoperative joint mobilization and accelerate functional recovery, both clinically critical outcomes. We therefore tested the hypothesis that a single preoperative oral dose of 1200 mg gabapentin improves postoperative analgesia and postoperative knee mobilization after anterior cruciate ligament repair under general anesthesia.

Methods

With approval of the local ethics committee and written informed consent, we studied ASA physical status I-II patients. All were scheduled to undergo elective arthroscopic anterior cruciate ligament repair using hamstring autograft under general anesthesia.

Exclusion criteria included age younger than 18 yr or older than 65 yr, obesity (>130% of ideal body weight), surgery performed with regional anesthesia, history of chronic pain, regular medication with analgesics, analgesic use within 24 h of surgery, drug or alcohol abuse, psychiatric disorders, inability to use patient-controlled analgesia (PCA), cardiovascular, renal, or hepatic diseases, and contraindications to gabapentin.

The evening before surgery, patients were instructed in the use of the 100-mm visual analog scale (VAS): a pain VAS (0 = no pain to 100 = worst imaginable pain) and an anxiety VAS (0 = no anxiety to 100 = worst imaginable anxiety). During this visit, the PCA device (3300 PCAS; Graseby, Watford, UK) was also explained to patients.

On the day of surgery, patients were assigned randomly, in a double-blind fashion, via a random-number table to receive 1200 mg gabapentin (gabapentin group) or an identical-looking placebo (control group) orally 1-2 h before surgery ($n = 20$ per group). Personnel involved in patient management and data collection were unaware of the group assignment.

No sedative premedication other than gabapentin was given. Anesthesia was induced with propofol at an initial target effect-site concentration of 5 $\mu\text{g}/\text{mL}$ (i.e., 2 mg/kg), followed by atracurium 0.5 mg/kg to facilitate orotracheal intubation. Remifentanyl was given at a target effect-site concentration of 4 ng/mL (i.e., 1 $\mu\text{g}/\text{kg}$ over 30 s) 1 min before orotracheal intubation. General anesthesia was maintained with a continuous infusion of propofol (target effect-site concentration of 2-6 $\mu\text{g}/\text{mL}$, i.e., 60-200 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), which was titrated to maintain Bispectral Index (BIS) between 45 and 55 and heart rate and mean arterial blood pressure within 20% of preoperative baseline, remifentanyl at a target effect-site concentration of 2 ng/mL (i.e., 0.1 $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and 50% N_2O in oxygen during

controlled ventilation. Thirty minutes before the anticipated end of surgery, a 0.1-mg/kg bolus of morphine was given IV. At skin closure propofol, remifentanyl, and N_2O were discontinued.

After tracheal extubation, patients were transferred to the postanesthetic care unit (PACU) until they achieved a modified Aldrete score of 9 on 2 sequential measurements at 10-min intervals. They were then discharged to the ward. Analgesia in the PACU was initially provided by titrating morphine in increments of 3 mg every 5 min until the VAS pain score was ≤ 30 mm. Titration was stopped if the sedation score was >2 or the respiratory rate <12 breaths per min. Patients were also given access to a PCA device set to deliver 1-mg boluses of IV morphine with a lockout period of 5 min and no background infusion. This PCA regimen was continued for 48 h. Ketoprofen (Bi-Profenid; Aventis, Inc., Montrouge, France), 150 mg orally twice daily, was started the evening of surgery in all patients.

The physical therapist mobilized the operated knee 24 and 48 h after surgery at levels of motion up to 90° maximal knee flexion as tolerated by the patient. Patients also performed knee extension against gravity. Mobilizations were passive and active, and each session lasted 20 min. At the end of each session, patients performed maximally tolerated passive and active knee flexions and extensions. During these physical therapy sessions, analgesia was provided by IV PCA morphine. The study ended after 48 h.

Anxiety was assessed with VAS before induction of anesthesia in the operating room.

The total doses of propofol and remifentanyl, duration of surgery and anesthesia, temperature at the end of surgery, and any intraoperative anesthetic or surgical complications were recorded. Recovery times were defined from the end of surgery. Emergence time to awakening (i.e., opening eyes on verbal command) was evaluated at 1-min intervals. Times to spontaneous ventilation recovery and orotracheal extubation were also noted.

Pain was measured with VAS at admission to the PACU and then hourly for 3 h. Pain was also evaluated at 4-h intervals on the surgical ward for 48 h and before and after mobilization.

Degrees of first passive and active knee flexions and extensions, and maximal degrees of passive and active knee flexions and extensions tolerated by each patient were recorded at the end of physical therapy sessions. PCA morphine consumption during the knee mobilization sessions was recorded by the physical therapist.

The time that elapsed between the end of surgery and patients' first request for analgesic medication was recorded, as was morphine consumption during IV titration. PCA morphine requirements were recorded hourly for 3 h and then every 4 h for 48 h.

Sedation scores and side effects were recorded before and after surgery. Sedation was measured on a numeric scale of 0-3 (0 = patient fully awake; 1 = patient somnolent and responsive to verbal commands; 2 = patient somnolent and responsive to tactile stimulation; and 3 = patient asleep and responsive to painful stimulation). We also specifically evaluated potential side effects, including lightheadedness, drowsiness, headache, decreased coordination, visual disturbances, nausea and vomiting (treated by IV boluses of droperidol 0.5 mg), and respiratory depression (defined as a sedation score >1 and a respiratory rate <10 breaths/min).

Maximal active knee flexion was considered the primary end-point. The secondary end points were VAS pain scores, morphine consumption, and VAS anxiety scores. Our sample size estimate was based on the expected differences in maximal active knee flexion at day one. In a previous study (14), we observed that the maximal active knee flexion after anterior cruciate ligament repair was 62° with a SD of 11°. A sample size estimate indicated that 19 patients per group would give a power of 80% at an α level of 0.05 for detecting a difference in 10° in maximal active knee flexion. The study size was thus prospectively set of 40 patients ($n = 20$ per group).

Morphometric and demographic characteristics of the patients, clinical variables, cumulative and hourly doses of morphine over 48 h, and amplitude of knee flexions in the gabapentin and control groups were compared with unpaired, two-tailed Student's *t*-test. VAS pain intensity scores were analyzed by two-way repeated-measures analysis of variance and *post hoc* comparisons at various time points using Bonferroni's type I error correction for multiple tests of significance. Because maximal amplitude of knee flexion and morphine consumption did not follow a normal distribution, the Mann-Whitney *U*-test was used for these two outcomes. χ^2 tests were used to compare the incidence of side effects. Results are expressed as mean \pm SD. $P < 0.05$ was considered statistically significant.

Results

Forty patients, 20 per group, were enrolled in the study. No patient was excluded. The two groups were comparable with respect to demographic and morphometric characteristics, duration of surgery, and intraoperative doses of propofol and remifentanyl (Table 1). Preoperative VAS anxiety scores were lower in the gabapentin group than in the control group (28 ± 16 versus 66 ± 15 mm, respectively; $P < 0.0001$). Heart rate, systolic and diastolic blood pressures, and BIS values were similar in the groups (data not shown). The times from the end of surgery until spontaneous

Table 1. Patient Characteristics and Intraoperative Data

	Control ($n = 20$)	Gabapentin ($n = 20$)
Gender (M/F)	13/7	14/6
Age (yr)	31 ± 8	31 ± 8
Weight (kg)	70 ± 14	69 ± 12
Height (cm)	174 ± 9	171 ± 8
Length of surgery (min)	79 ± 23	81 ± 34
Length of anesthesia (min)	115 ± 23	117 ± 33
Total propofol dose (mg)	846 ± 345	825 ± 270
Total remifentanyl dose (μ g)	675 ± 271	641 ± 241
Time to spontaneous ventilation (min)	5 ± 2	5 ± 2
Time to awakening (min)	7 ± 2	8 ± 2
Time to tracheal extubation (min)	8 ± 2	8 ± 2

All values, except for male/female ratio, are mean \pm SD.

ventilation, awakening, and tracheal extubation were also comparable in the two groups (Table 1).

First and maximal passive and active knee flexions were significantly more extensive in the gabapentin than in the control group at 24 h. These differences persisted at 48 h despite better knee flexions at 48 h than at 24 h in both groups. Knee extensions were comparable in the 2 groups during the 2 postoperative days, except at 24 h when the gabapentin group had greater first active knee extension (Table 2).

VAS pain scores during the initial hour of recovery were greater in the control group than in the patients given gabapentin; however, VAS pain scores were subsequently similar in the groups (Fig. 1).

The time until the first request for analgesia (morphine) in the PACU was longer in the gabapentin than in the control group (Table 3; $P = 0.0007$). More patients in the control group required morphine titration in the PACU (19 versus 9; $P < 0.001$), and the gabapentin group required less morphine during this titration (6.8 ± 5.8 versus 12.8 ± 3.6 mg, respectively; $P < 0.01$). Cumulative morphine consumption in the first 48 h, including morphine titrated in the PACU, was halved in the gabapentin group (Table 3; $P < 0.0001$). Incremental morphine consumption during the first postoperative 48 h was less in the gabapentin than in the control patients (Fig. 2; $P < 0.001$) with significant differences at all time periods except 36-48 elapsed hours.

Before induction of anesthesia, no patient in either group reported sedation (sedation score of 0 in all patients except in one gabapentin patient who had a sedation score of 1) or side effects. The incidence of postoperative side effects was comparable in the groups: 3 patients in each group complained of nausea, the distribution of sedation scores was similar in the 2 groups, and sedation scores were < 2 in all patients.

Table 2. Knee Flexion During Physiotherapy

	Postoperative Day 1			Postoperative Day 2		
	Control	Gabapentin	<i>P</i> value	Control	Gabapentin	<i>P</i> value
First passive flexion (°)	50 ± 17	70 ± 14	0.001	65 ± 15	75 ± 14	0.015
First active flexion (°)	44 ± 19	65 ± 14	0.001	62 ± 16	71 ± 17	0.034
Maximal passive flexion (°)	68 ± 15	78 ± 10	0.022	81 ± 7	85 ± 11	0.030
Maximal active flexion (°)	64 ± 18	76 ± 9	0.020	77 ± 11	84 ± 12	0.007
First passive extension (°)	-5 ± 5	-2 ± 3	0.070	-2 ± 5	-1 ± 2	0.107
First active extension (°)	-7 ± 9	-2 ± 3	0.022	-3 ± 6	-1 ± 4	0.158
Maximal passive extension (°)	-1 ± 3	0 ± 1	0.180	0 ± 2	0 ± 1	0.330
Maximal active extension (°)	-3 ± 5	-1 ± 2	0.205	-1 ± 3	0 ± 2	0.184

Results presented as mean ± SD.

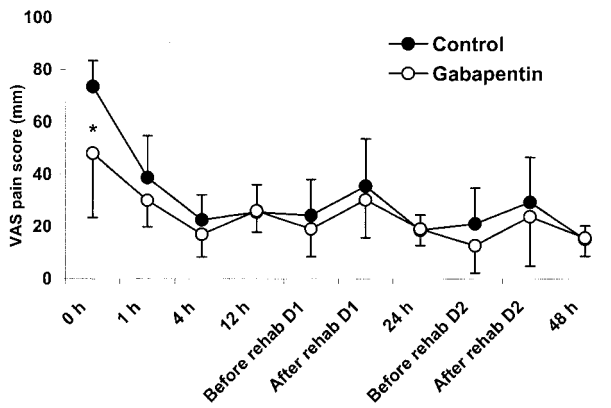


Figure 1. Visual analog pain scale (VAS) scores during the 48 postoperative hours and before and after physiotherapy on days 1 and 2. Time zero is admission to the postanesthesia care unit. Results are presented as mean ± SD. *Statistically significant differences between treatment groups.

Discussion

Unsurprisingly, postoperative analgesics are opioid-sparing; however, they typically do not significantly improve pain scores or functionality. Our primary result was that simply giving oral gabapentin as premedication not only reduced postoperative morphine consumption but also simultaneously enhanced postoperative analgesia and improved knee mobilization. These effects of gabapentin persisted for 2 days; this far exceeds the pharmacological duration suggested by the drug's 5-9-hour half-life (5).

The effects of a preoperative dose of gabapentin on postoperative pain control was evaluated in previous recent studies as well: two performed in breast surgery patients (8,9), two in abdominal hysterectomy patients (10,12), one in patients having spinal surgery (11), and one in ear-nose-throat surgery (13). The morphine-sparing effect varied between 30% and 62%, and pain at rest and during mobilization was reduced (8,9,11-13) in all but one study (10). Our findings are thus consistent with previous results. Pain scores at rest were significantly reduced only on arrival to the PACU in our patients. The most likely explanation is

simply that patients were able to rapidly titrate morphine to obtain adequate and comparable analgesia. Pain at rest and with movement was comparable in each group during physiotherapy sessions. However, the maximal degree of active knee flexion tolerated by the patients was considerably more extensive in the gabapentin group, indicating that the drug was an effective adjunct.

Our study is the first to assess the influence of preoperative gabapentin on joint function. Maximal knee flexion during physiotherapy was our primary outcome measure because it represents an important variable in long-term functional recovery after knee surgery. Functional recovery is accelerated by early and intensive physiotherapy and extensive postoperative knee flexion that prevents deleterious effects of joint immobilization (15) after knee arthroplasty (16) and anterior cruciate ligament repair (17). Inadequate analgesia during joint movement limits mobilization of the knee joint, thus impairing functional recovery. Our major finding is thus that preoperative gabapentin increases movement amplitude, presumably by preventing movement-evoked pain.

Pain at rest and evoked pain caused by surgery are likely subtended by different mechanisms (18). Evoked pain during movement is enhanced by central neuronal sensitization (18), and the persistent gabapentin effects observed in our study were likely the result of preoperative gabapentin preventing central nervous system sensitization. We have previously reported similar benefits with the same type of surgery with another antihyperalgesic drug, ketamine, administered as a single intraoperative small dose (14). However, preoperative gabapentin was more effective in increasing early postoperative knee flexion than intraoperative small dose ketamine.

The mechanism of antihyperalgesic action of gabapentin remains largely unknown. Although it is a structural analog of gamma-aminobutyric acid (GABA), it does not act via GABA_B receptors or other known neurotransmitter receptors such as NMDA (5). It might bind to the α_{2δ} subunit of voltage-dependent calcium channels (5). As in animal studies (19), clinical

Table 3. Cumulative Morphine Consumption at 24 and 48 Hours, and Time to First Morphine Request in the Postanesthesia Care Unit

	Control	Gabapentin	P value
First morphine request (min)	1 ± 2	16 ± 28	0.001
Morphine consumption 24 h (mg)	48 ± 19	21 ± 12	<0.001
Morphine consumption 48 h (mg)	69 ± 40	29 ± 22	<0.001

Results presented as mean ± SD.

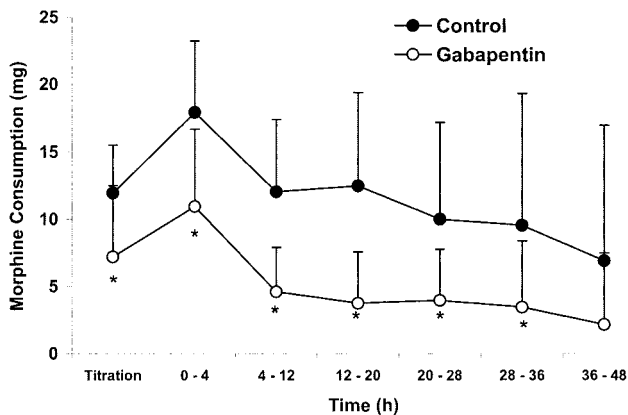


Figure 2. Incremental postoperative morphine consumption during 48 postoperative hours was significantly less in the gabapentin group than in the control group ($P < 0.001$). All time points differed significantly except 36–48 postoperative hours. Results are presented as mean ± SD.

studies show some similarities in the reduction of hyperalgesia between gabapentin and NMDA receptor antagonists (6). Such parallel results suggest that the $\alpha_{2\delta}$ subunit of voltage-dependent calcium channels are up-regulated in inflammatory pain processing, like the NMDA receptors, and would contribute, like NMDA receptors, to the development and maintenance of hyperalgesia. Up-regulation of the $\alpha_{2\delta}$ subunit of calcium channels in the central nervous system have already been shown in rats with nerve ligation-induced neuropathy (20). This unique binding to the $\alpha_{2\delta}$ calcium subunit, which is located presynaptically in the superficial lamina of spinal cord, explains the reduction of neurotransmitter release by gabapentin and thus its antinociceptive effect (5). However, other mechanisms have been proposed to explain the anti-allodynic action of gabapentin, such as activation of adenosine 5'-triphosphate-sensitive K^+ channels or inhibition of nitric oxide synthase (5).

The gabapentin effects that we observed may be also explained by an interaction between gabapentin and opioids. Gabapentin increases the analgesic effect of morphine in healthy volunteers (21), and studies suggest that gabapentin and morphine have a synergistic analgesic interaction (22). In rats, moreover, gabapentin prevents development of morphine tolerance and partially reverses established tolerance (23). A number of mechanistic hypotheses explaining

gabapentin-opioid interactions have been proposed (23), including gabapentin inhibition of glutamate release, nitric oxide synthase activation, dynorphin-induced allodynia, or postsynaptic calcium entry.

During surgery in the present study, we used remifentanyl, which can induce acute opioid tolerance and postoperative opioid-withdrawal hyperalgesia (24). Our findings might thus have resulted from a suppression of hyperalgesia caused by the withdrawal from intraoperative remifentanyl as well as the prevention of surgery-induced hyperalgesia. Even if this hypothesis is correct, gabapentin clearly has effects that are independent from those of remifentanyl, as reductions in pain and opioid consumption with gabapentin have been observed in patients who did not receive intraoperative opioids (9).

Another important finding of our study was that gabapentin produced a statistically significant and clinically important improvement in preoperative anxiety scores. Gabapentin has been reported as an anxiolytic drug in previous studies (7,25,26). For example, it was effective in treating anxiety associated with panic disorders (7,26,27). Recently, de-Paris et al. (27) demonstrated that gabapentin attenuated anxiety associated with simulated public speaking in volunteers. This disorder may be related to the preoperative anxiety state. The interest in using gabapentin preoperatively to decrease preoperative anxiety is a result of its limited side effects in comparison with other standard mood-stabilizing drugs. Moreover, gabapentin seems anxiolytic without exerting amnesic effects (28). However, additional study is necessary to fully validate these promising aspects of gabapentin's pharmacology.

Reducing preoperative anxiety with gabapentin may have contributed to the improved postoperative pain and to the reduced morphine use because there is a possible association between preoperative anxiety and postoperative pain (29,30). Whether preoperative anxiolysis without coping behavior and preoperative information has an impact on the postoperative pain response and morphine requirements, however, remains controversial (30).

The use of gabapentin might be limited by its previously reported side effects, e.g., dizziness, somnolence, confusion, and ataxia (5). However, no adverse effects were noted in our study.

In summary, our results indicate that premedication with 1200 mg oral gabapentin decreases preoperative anxiety, reduces postoperative morphine consumption by 50%, and improves early knee flexion after anterior cruciate ligament repair under arthroscopy—and does so without producing side effects. Improved joint mobility and reduced opioid consumption probably result from the ability of gabapentin to prevent postoperative hyperalgesia and central sensitization.

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