

Pre-emptive gabapentin significantly reduces postoperative pain and morphine demand following lower extremity orthopaedic surgery

Montazeri K, Kashefi P, Honarmand A

ABSTRACT

Introduction: Gabapentin has demonstrated analgesic effects in clinical trials as a pre-emptive analgesic and in acute postoperative pain management. This study was conducted to evaluate whether the pre-emptive use of gabapentin could reduce postoperative pain and morphine consumption in patients after lower extremity orthopaedic surgery.

Methods: 70 ASA I and II patients were randomly assigned to receive 300 mg gabapentin or placebo in a double-blind manner two hours before surgery under general anaesthesia. Postoperatively, the pain was assessed on a visual analogue scale (VAS) at 2, 4, 12, and 24 hours at rest. Morphine 0.05 mg/kg intravenously was used to treat postoperative pain on patients' demand. Total morphine consumption in the first 24 hours after surgery was also recorded.

Results: Patients in the gabapentin group had significantly lower VAS scores at all time intervals of 2, 4, 12, and 24 hours, than those in the placebo group (respectively, 55.50 [mean] +/- 15.80 [standard deviation], 57.30 +/- 19.30, 45.74 +/- 16.00, 44.60 +/- 17.64, versus 72.30 +/- 14.00, 70.50 +/- 18.13, 62.00 +/- 23.32, 66.50 +/- 25.70; p-value is less than 0.05). The total morphine consumed after surgery in the first 24 hours in the gabapentin group (15.43 +/- 2.54) was significantly less than in the placebo group (17.94 +/- 3.00; p-value is less than 0.05).

Conclusion: Pre-emptive use of gabapentin 300 mg orally significantly decreases postoperative pain and rescue analgesic

requirements in patients who undergo lower extremity orthopaedic surgery.

Keywords: analgesic requirement, gabapentin, morphine demand, orthopaedic procedures, pain management, postoperative pain

Singapore Med J 2007; 48(8):748-751

INTRODUCTION

Gabapentin, a new antiepileptic agent, has demonstrated potent antihyperalgesic properties in preclinical and clinical studies, without affecting acute nociception.^(1,2) In animal studies, gabapentin exhibits antihyperalgesic actions induced by inflammation.^(3,4) Intrathecal gabapentin has also been shown to enhance the antinociceptive effect of intrathecal morphine in the rat tail-flick test.⁽⁵⁾ In rats, the antihyperalgesic effect of gabapentin was of the same magnitude as that of ibuprofen, given either systemically or intrathecally.⁽⁶⁾ In human volunteers, gabapentin demonstrated substantial inhibitory effects on the development and established secondary allodynia and hyperalgesia resulting from sensitisation of the skin with heat and capsaicin.⁽⁷⁾ The magnitude of this effect was comparable with the effect observed with remifentanyl.⁽⁸⁾

The rationale behind pre-emptive analgesia is that antinociceptive treatment started before surgery is more effective in reducing postoperative pain than treatment started in the early postoperative period.⁽⁹⁾ Gabapentin has demonstrated analgesic effects in clinical trials as a pre-emptive analgesic and in acute postoperative pain management; however, experience with gabapentin is limited.⁽¹⁰⁻¹²⁾ There has not been a separate study about the pre-emptive use of gabapentin in orthopaedic surgery. We therefore designed the present study to investigate whether pre-emptive use of gabapentin 300 mg orally could reduce postoperative pain and morphine consumption in the initial 24 hours after orthopaedic surgery on the lower extremities.

Department of
Anaesthesiology
and Intensive Care
Medicine,
School of Medical
Sciences,
Isfahan University,
Isfahan,
Iran

Montazeri K, MD
Associate Professor

Kashefi P, MD
Associate Professor

Honarmand A, MD
Assistant Professor

Correspondence to:
Dr Azim Honarmand
Tel: (98) 913 110 2327
Fax: (98) 311 236 1594
Email: honarmand@
med.mui.ac.ir

METHODS

The study was approved by the ethic committees of the participating institutions. Written informed consent was obtained from each patient. The inclusion criteria were: (1) age 16–70 years; (2) ASA physiological status I–II; (3) duration of surgery between 1.5–2 hours; and (4) scheduled for knee arthroscopy. The exclusion criteria were: (1) known allergy against gabapentin; (2) epilepsy; (3) previous treatment with gabapentin; (4) chronic pain syndrome; (5) psychiatric disorder; (6) substance abuse; (7) impaired kidney or liver function; and (8) patients who had received analgesics within 48 hours before surgery. No premeditation was given to the patients.

The patients were divided into two groups with the use of a table of random numbers. A physician from a department not involved in this study prepared the drug-containing bags, each containing one capsule according to the list. In group I, the bag contained one 300 mg capsule of gabapentin. In group II the bag contained one placebo capsule. The size and shape of the capsules for both groups looked similar. The medication was given to the patients about two hours before induction of anaesthesia. The name of the study and the running number of the patient were stated on the bags. For safety reasons, the randomisation list, including the contents of the study bag of each patient, was kept in the recovery room of each operation theatre. During the preanaesthetic round, the patients were instructed on the use of a visual analogue scale (VAS, range 0–10 cm). Anaesthesia was induced with thiopental 5 mg/kg, fentanyl 2 µg/kg, and atracurium 0.6 mg/kg. Morphine 0.1 mg/kg was given before the start of the surgery. Anaesthesia was maintained with isoflurane 1.25% and 50% nitrous oxide in oxygen and intermittent atracurium when indicated. Monitoring during anaesthesia comprised of continuous electrocardiography, heart rate, pulse oximetry, noninvasive arterial pressure, measurement of the end tidal CO₂ (Capnograph, Datex, Helsinki, Finland), and measurement of the inspiratory isoflurane concentrations. All these parameters were recorded at five-minute intervals.

After completion of surgery, neuromuscular blockade was reversed with atropine 0.02 mg/kg and neostigmine 0.04 mg/kg, and patients were extubated when adequate spontaneous ventilation was established. Fitness for discharge was evaluated using a modification⁽¹³⁾ of the Aldrete and Krouliks scoring system.⁽¹⁴⁾ The time elapsed between the discontinuation of anaesthesia and a recovery score of 13 was considered the recovery duration, and the values were compared between both groups. After surgery, a physician, who was not the part of the anaesthesia team, recorded the pain score at 2, 4, 12,

Table I. Demographical and clinical variables (mean + SD).

Variable	Gabapentin (n = 35)	Placebo (n = 35)
Age (years)	34.7 ± 18.1	34.6 ± 17.8
Weight (kg)	64.8 ± 11.5	63.2 ± 10.3
Height (cm)	164.6 ± 8.3	165.2 ± 9.4
Gender (male:female)	26:9	28:7
Duration of anaesthesia (min)	114.8 ± 6.9	112.3 ± 5.8
Duration of surgery (min)	105.1 ± 7.2	103.3 ± 6.4
Intraoperative fentanyl dose (µg)	125.4 ± 6.7	126.7 ± 5.8
Intraoperative morphine dose (mg)	6.3 ± 3.4	6.1 ± 4.6

No significant difference between groups.

and 24 hours after surgery using the VAS (where 0 = no pain and 10 = worst possible pain) at rest. At the same time points, the patients were also asked to evaluate possible side-effects of the premedication drug (e.g. somnolence, nystagmus, tremor, diplopia and nausea). The times from the end of the surgery until the first bolus of morphine administered on demand were recorded. Patients received morphine 0.05 mg/kg IV on demand. The total rescue analgesic requirement in the first 24 hours was recorded.

The data were entered into the Statistical Package for Social Sciences version 10.0 (SPSS Inc, Chicago, IL, USA). On the assumption that a 20% difference in morphine consumption between the groups would be of clinical interest, the study required 35 patients in each group to have a power $\beta = 80\%$ and $\alpha = 0.05$. The mean and standard deviation (SD) of the pain score for the two groups at time intervals of 2, 4, 12, and 24 hours were calculated and analysed with two-factor ANOVA for repeated measures. Similarly, total morphine consumption in each group was compared with unpaired *t*-tests. A *p*-value of < 0.05 was considered significant.

RESULTS

70 patients consented to participate in the study. There was no difference in age, sex, body weight, and duration of anaesthesia between the two groups (Table I). In comparison with the placebo group, patients in the gabapentin group had significantly lower VAS scores at all time intervals of 2, 4, 12, and 24 hours during the study period and required significantly less morphine for postoperative pain management (Table II). There was a significant difference between the two groups in the first time of patients' demand for morphine administration after surgery (31.57 ± 15.90 min in the gabapentin group versus 26.71 ± 7.10 min in the placebo group, $p < 0.05$). There was no significant

Table II. Visual analogue scale scores and total morphine consumption (mean \pm SD).

Groups	2 hr	4 hr	12 hr	24 hr	Total 24-hr morphine consumption (mg)
Gabapentin	55.50 \pm 15.80*	57.30 \pm 19.30*	45.74 \pm 16.00*	44.60 \pm 17.64*	15.43 \pm 2.54*
Placebo	72.30 \pm 14.00	70.50 \pm 18.13	62.00 \pm 23.32	66.50 \pm 25.70	17.94 \pm 3.00

*p < 0.05 vs placebo group

difference in the recovery duration between the two groups. Postoperatively, the incidence of adverse effects (nausea six versus five, vomiting four versus three, fatigue one versus none, light-headedness one versus none, and dizziness one versus none) was similar in the gabapentin and placebo groups.

DISCUSSION

The present study has demonstrated the significant analgesic effect of the pre-emptive use of 300 mg oral gabapentin after orthopaedic surgery on the lower extremities. A decrease in total analgesic consumption along with a significant decrease in VAS pain scores were found in patients who received gabapentin two hours before surgery, in comparison to patients who received a placebo. Gabapentin is an antiepileptic drug and a structural analogue of gamma amino butyric acid (GABA).⁽¹⁵⁾ After a single oral dose of 300 mg, mean maximum plasma concentrations are attained in 2-3 hours.⁽¹⁵⁾ Though the exact mechanism of gabapentin action is not known, proposed mechanisms include its ability to: increase the concentration and the rate of synthesis of GABA in the brain; bind with high affinity to binding sites in brain tissues that are associated with an auxiliary subunit of voltage sensitive calcium channels ($\alpha_2\delta$ subunits); reduce the release of monoamine neurotransmitters; inhibit voltage-activated sodium channels; and increase serotonin concentrations in the human blood.^(16,17)

The pre-emptive administration of gabapentin approximately two hours before surgery appears optimal in order to attain maximal plasma concentrations at the time of surgical stimuli. It has also been demonstrated that a single dose of 600 mg of gabapentin added to 60 mg slow-release morphine increases pain tolerance to the cold pressure test in humans. Though the cold pressure test is a test of short duration and tolerance to pain, and is not synonymous with analgesic efficacy, the available data are useful when planning the treatment of acute pain with gabapentin.⁽¹⁸⁾ It has also been demonstrated that a 600 mg single dose of gabapentin enhanced the effect of morphine, but side effects appeared in approximately 40% of volunteers when these drugs were used concomitantly.⁽¹⁸⁾ Another study of 22 human volunteers who received 1,200 mg of

gabapentin or placebo in a double-blind, randomised cross-over fashion on two separate study days, demonstrated reduced primary mechanical allodynia in acute inflammation following a first degree thermal injury, suggesting that gabapentin had clinical potential in the treatment of postoperative pain.⁽¹⁹⁾ The analgesic efficacy of gabapentin when it was used as a pre-emptive analgesic (one hour before the surgical stimulus) has also been demonstrated in surgical patients by Dirks et al, who found a substantial reduction in postoperative morphine consumption without significant side effects.⁽¹⁾

In summary, although the exact mechanism of the action of gabapentin is not well understood, clinical and experimental studies have demonstrated its analgesic efficacy and safety in physiological as well as pathological pain. Our clinical study on postoperative pain demonstrates that a pre-emptive 300 mg oral dose of gabapentin reduces the pain scores and morphine requirements in the immediate postoperative period in patients undergoing lower limb surgery.

REFERENCES

1. Dirks J, Fredensborg BB, Christensen D, et al. A randomized study of the effects of single-dose gabapentin versus placebo on postoperative pain and morphine consumption after mastectomy. *Anesthesiology* 2002; 97:560-4.
2. Mao J, Chen LL. Gabapentin in pain management. *Anesth Analg* 2000; 91:680-7.
3. Carlton SM, Zhou S. Attenuation of formalin-induced nociceptive behaviors following local peripheral injection of gabapentin. *Pain* 1998; 76:201-7.
4. Field MJ, Oles RJ, Lewis AS, et al. Gabapentin (neurontin) and S-(+)-3-isobutylgaba represent a novel class of selective antihyperalgesic agents. *Br J Pharmacol* 1997; 121:1513-22.
5. Shimoyama N, Shimoyama M, Davis AM, Inturrisi CE, Elliott KJ. Spinal gabapentin is antinociceptive in the rat formalin test. *Neurosci Lett* 1997; 222:65-7.
6. Yoon MH, Yaksh TL. Evaluation of interaction between gabapentin and ibuprofen on the formalin test in rats. *Anesthesiology* 1999; 91:1006-13.
7. Dirks J, Petersen KL, Rowbotham MC, Dahl JB. Gabapentin suppresses cutaneous hyperalgesia following heat-capsaicin sensitization. *Anesthesiology* 2002; 97:102-6.
8. Petersen KL, Jones B, Segredo V, Dahl JB, Rowbotham MC. Effect of ramifenitil on pain and secondary hyperalgesia associated with the heat-capsaicin sensitization model in healthy volunteers. *Anesthesiology* 2001; 94:15-20.
9. Kissin I. Preemptive analgesia. Why its effect is not always obvious. *Anesthesiology* 1996; 84:1015-9.
10. Chiaretti A, Viola L, Pietrini D, et al. Preemptive analgesia with tramadol and fentanyl in pediatric neurosurgery. *Childs Nerv Syst* 2000; 16:93-9.
11. Naguib M, Seraj M, Attia M, et al. Perioperative antinociceptive effects of tramadol. A prospective, randomized, double-blind comparison with morphine. *Can J Anaesth* 1998; 45:1168-75.

12. Fassoulaki A, Patris K, Sarantopoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. *Anesth Analg* 2002; 95:985-91.
13. Lenhardt R, Marker E, Goll V, et al. Mild intraoperative hypothermia prolongs postanesthetic recovery. *Anesthesiology* 1997; 87:1318-23.
14. Aldrete JA, Kroulik D. A postanesthetic recovery score. *Anesth Analg* 1970; 49:924-34.
15. Goa KL, Sorkin EM. Gabapentin. A review of its pharmacological properties and clinical potential in epilepsy. *Drugs* 1993; 46:409-27.
16. Taylor CP, Gee NS, Su TZ, et al. A summary of mechanistic hypotheses of gabapentin pharmacology. *Epilepsy Res* 1998; 29:233-49.
17. Gee NS, Brown JP, Dissanayake VU et al. The novel anticonvulsant drug, gabapentin (neurontin), binds to the $\alpha 2\delta$ subunit of a calcium channel. *J Biol Chem* 1996; 271:5768-76.
18. Eckhardt K, Ammon S, Hofmann U, et al. Gabapentin enhances the analgesic effect of morphine in healthy volunteers. *Anesth Analg* 2000; 91:185-91.
19. Werner MU, Perkins FM, Holte K, Pedersen JL, Kehlet H. Effects of gabapentin in acute inflammatory pain in humans. *Reg Anesth Pain Med* 2001; 26:322-8.

2007 SMJ Best Research Paper Awards

The Singapore Medical Association will be presenting awards for the Best Research Paper published in the Singapore Medical Journal (SMJ) in 2007. All original research papers that are published in the SMJ during the one year period from January 1, 2007 to December 31, 2007 will be considered for this award.

The following are the judging criteria:

- **The paper with the most potential impact on clinical practice**
- **Most rigorous study design/research methodologies**
- **Comprehensive data analysis and balanced discussion**
- **Data interpretation**

Distinguished members of the medical profession will be invited to serve on our panel of judges for selecting the winning papers.

The authors of the winning papers selected by our panel of judges will receive cash prizes for the first, second and third places. Prize winners will also receive a commemorative trophy and certificate.

We thank you for your support of the SMJ. The quality of our journal depends on the quality of your submissions.