



Perioperative gabapentin as a component of multimodal analgesia for postoperative pain after total knee arthroplasty

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Background: Total knee arthroplasty (TKA) causes considerable postoperative pain. This study investigated the analgesic effects of gabapentin on postoperative pain in patients undergoing unilateral TKA in Mongolia.

Methods: The study randomly assigned 95 patients with American Society of Anesthesiologists physical status class 1–3 scheduled for unilateral TKA into two groups. The treatment group ($n = 49$) was given gabapentin 600 mg 2 h preoperatively and gabapentin 300 mg in the evening for 3 days postoperatively. The control group ($n = 46$) was given identical looking placebo capsules. Pain using a visual analogue scale (VAS) and postoperative nausea and vomiting were assessed every hour postoperatively for 6 h and then every 3 h for the next 72 h. The total consumption of fentanyl in both groups was recorded at 24 and 48 h postoperatively.

Results: The very low VAS scores in both groups did not differ significantly. Patients in the treatment group used less fentanyl on the second day ($P = 0.001$). The incidence of nausea and vomiting were similar in both groups, except for the low incidence of nausea in the treatment group in the first 6 h postoperatively.

Conclusions: Perioperative gabapentin may be a component of a multimodal analgesia method because it reduced fentanyl consumption in patients who underwent TKA. However, the overall low VAS scores do not allow any firm conclusions. (*Anesth Pain Med* 2017; 12: 169–175)

Key Words: Gabapentin, Knee arthroplasty, Postoperative pain.

INTRODUCTION

Several studies have suggested the gabapentin has the potential to become a routine part of acute postoperative pain treatment. Patients with preoperative pain and poor postoperative pain management are at risk of developing prolonged postoperative pain, in up to 50% in some series [1]. In Mongolia, the demand for total knee arthroplasty (TKA) has increased, and TKA is recognized as causing significant postoperative pain [2]. International centers use multimodal balanced analgesia, including non-steroidal anti-inflammatory drugs, opioids via patient-controlled infusion pumps, local infiltration, and femoral nerve block [3]. In comparison, the medical supply system in Mongolia is underdeveloped, resulting in frequent shortages and inconsistent supplies of medicine. Patient-controlled analgesia (PCA) pumps, ultrasound access, nerve stimulators, and insulated needles for nerve blocks are seldom available. Furthermore, anesthesiologists are unfamiliar with multimodal analgesia and have inadequate practical training in peripheral nerve blockade. Hence, this study explored an option for multimodal analgesia based on a new medication that does not require additional equipment or complex procedures. We assessed the use of oral gabapentin as an adjuvant to multimodal analgesia in our country.

Gabapentin is an anticonvulsant that has antinociceptive and antihyperalgesic properties. It has a well-established role in the treatment of chronic pain. It is effective for neuropathic pain, such as diabetic neuropathy and postherpetic neuralgia [4,5]. Many meta-analyses and clinical trials have shown that perioperative gabapentinoid use has a significant opioid-sparing effect and probably improves postoperative pain scores relative to controls. Several studies have examined whether gabapentin treatment has the potential to become a routine part of acute

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post-surgical pain management [6-11]. However, a recent study suggested that gabapentin cannot prevent acute postoperative pain in TKA [12].

We recognized that with our current multimodal analgesia regimen, our patients rarely complain of postoperative pain, even on movement of the knee. As a measure of pain relief, we used the amount of fentanyl (background infusion and PCA bolus).

Therefore, this study examined the effect of gabapentin as a component of multimodal analgesia by comparing the pain scores using a visual analogue scale (VAS) and fentanyl use between the two groups. We also explored opioid-related adverse effects following TKA.

MATERIALS AND METHODS

This study was approved by the Ethics Committee of Mongolian National University of Medical Sciences (File No.: 13-16/2A 2013-05-10). All patients in the study provided written informed consent.

We calculated the sample size needed to find a difference in

fentanyl consumption (μg) when patients are treated with gabapentin compared with standard treatment. We set a statistical power of 80% at the 0.05 significance level and set a clinically acceptable margin for fentanyl consumption at 65 μg . This required 37 subjects in each group. The study size was increased to 50 patients per group to ensure that a sufficient number of patients were included that experienced nausea and vomiting as side effects. The study included TKA patients seen at the First Central Hospital of Mongolia between November 2013 and August 2015 with American Society of Anesthesiologists (ASA) class I-III; age 15-75 years; and body mass index (BMI) < 35 kg/m^2 . Out of 122 eligible patients scheduled for TKA during this period, 22 were excluded for the following reasons: diabetes mellitus, renal or hepatic insufficiency, preoperative opioid usage, peripheral neuropathy, required general anesthesia, were unable to use PCA, or declined participation in this study (Fig. 1). Consequently, 100 patients were enrolled and randomly assigned to control (placebo) and treatment (gabapentin) groups (Fig. 1).

Random assignment was carried out by choosing a sealed envelope from a transparent box that originally contained 50

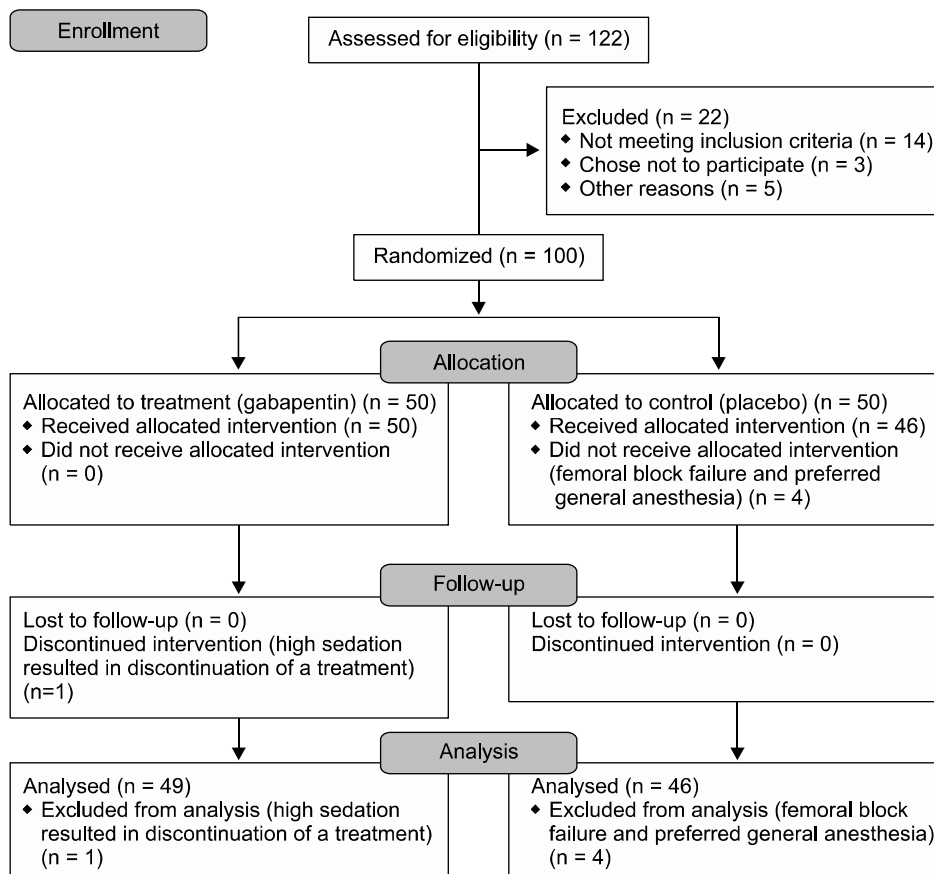


Fig. 1. Patient enrollment and study flow.

envelopes for each group. The senior anesthesia nurse picked the envelope 1 day prior to surgery and presented the result of the selection to the pharmacist who provided the tablets to the unit nurse who was blinded to the results. The pharmacist had no access to or interaction with the patients. The surgeons, anesthesiologists, unit nurses, and patients were all blinded during the study.

This study examined the effects of gabapentin on postoperative pain following TKA and any nausea and vomiting in the two groups. The treatment group was given 600 mg of gabapentin (Tebantin 300 mg, Gideon Richter, Budapest, Hungary) 2 h before the surgery and 300 mg of gabapentin at 9:00 p.m. for 3 days postoperatively. Given that all TKA surgeries are planned surgeries, the hospital schedules them during the first half of the day. The control (placebo) group was given identical appearing placebo capsules at the same times as those prescribed for the treatment group.

Perioperative preparations

1. Anesthesia

All of the patients underwent spinal anesthesia. Intrathecal anesthesia was induced in the sitting position at the L3-L4 or L4-L5 level using a 27-gauge Quincke needle via a paramedian approach into the subarachnoid space with 12–14 mg of isobaric bupivacaine (depending on the height and age of the patient) and 20–25 µg fentanyl. The patients were sedated with fentanyl 25 µg intravenously (IV). If the patient complained of pain during the procedure, an additional 25 µg of fentanyl and diazepam 3–4 mg IV were given. If the patient requested deeper sedation during the surgery, an additional 2–4 mg diazepam was given. Oxygen was given at 2–3 L/min via nasal cannula throughout the surgery. All patients were monitored using an electrocardiogram, pulse oximetry, and non-invasive blood pressure. During the surgery, if the mean arterial pressure fell below 60 mmHg, which we consider borderline hypotension, it was corrected by administering ephedrine 5–10 mg IV.

2. Surgery

All operations were performed by the same surgeon. A tourniquet was applied around the thigh before the start of surgery and deflated just before wound closure. The rehabilitation protocol in both groups was identical.

3. Pain control modalities

Before anesthesia, all patients received a single-shot femoral nerve block. Following sterile preparation and draping of the groin on the operative side, a femoral nerve block was performed with a 21–22 gauge needle (Stimuplex A; B.Braun, Germany) introduced 1–1.5 cm lateral to the femoral artery. A nerve stimulator (Stimuplex HNS-12; B.Braun, Germany) was set at 2 Hz and 2 mA. When quadriceps contraction and upward movement of the patella were detected, the current was decreased and the needle position was optimized for contraction at a current output of 0.5 mA. Then, bupivacaine 0.5%–20 ml was injected slowly. Metamizole 1,000 mg IV and diclofenac sodium 75 mg intramuscularly (IM) were administered 1 h before the skin incision.

Metamizole and diclofenac sodium are the most commonly used and affordable analgesics in Mongolia. Postoperative analgesia comprised metamizole 1,000 mg IV and diclofenac sodium 75 mg IM three times a day and PCA with a background infusion of fentanyl 2 ml/h (20 µg/h) and 5 µg bolus with a lock-out time of 15 min.

Due to the anticipated low pain scores, we measured both the fentanyl consumption and VAS score as the main outcome factors for analysis. The VAS ranged from 0 (no pain) to 10 (worst pain imaginable), and was assessed at rest and during mobilization. Patients and caregivers were instructed on the VAS. Postoperative fentanyl consumption was calculated based on the recorded start and end times of PCA and a rate of 20 µg/h; the total background dose was calculated by multiplying the number of hours by 20 µg. For example, if the PCA started at 10 a.m. ended after 36 h, the total dose was 720 µg (36 h × 20 µg/h). In addition, the bolus fentanyl dose was measured using the time records of every 5 µg bolus of fentanyl. For example, if the patient pushed the PCA pump button five times, the total fentanyl bolus equals 25 µg. The side effects of nausea and vomiting were determined from the nursing charts. The VAS and nausea and vomiting were recorded every hour postoperatively for 6 h, and then every 3 h for the next 72 h.

Postoperative nausea and vomiting was treated with ondansetron 4 mg IV repeated every 6 h if required; if not effective, droperidol 1.25 mg IV was offered. Routine monitoring was performed in the recovery room for 2–3 h.

Data processing and statistical analysis

Data entry and analysis was performed using SPSS 17

(SPSS, IBM Corp., USA). Descriptive statistics were used to describe the characteristics of the two groups vis-a-vis age, gender, BMI, duration of anesthesia, and surgery. The difference in pain between the groups measured using the VAS and fentanyl consumption was analyzed based on descriptive statistics and statistical significance was tested using the t-test. Bonferroni's correction was performed for repeated measures data. The frequencies of postoperative nausea and vomiting (PONV) were compared using the chi-square test.

RESULTS

The two patient groups did not differ significantly in age, gender, BMI, duration of anesthesia, or surgery apart from the ASA class (Table 1).

Pain scores analyzed using the VAS revealed a very low level of pain overall, with the mean VAS score often below 1. As expected, the VAS was marginally higher during

movement. In addition, the VAS was consistently higher in the control group at all times starting 6 h postoperatively. After applying Bonferroni's correction for repeated measures, the VAS score differed significantly at rest at 24–47 h and with movement at all times beginning 6 h postoperatively (Table 2).

On the first postoperative day, the background fentanyl dose was $485.1 \pm 13.5 \mu\text{g}$ for the treatment group and $491.7 \pm 17.5 \mu\text{g}$ for the controls ($P = 0.053$). On the second day, it was reduced to 349.7 ± 83.2 for the treatment group and 405.2 ± 64.1 for the controls ($P = 0.001$). The bolus fentanyl dose was 12.3 ± 20.7 for the treatment group and 14.1 ± 17.6 ($P = 0.656$) for the controls, and did not differ significantly (Table 3).

In terms of side effects, the incidence of PONV was compared between the two groups (Table 4). Incidence of nausea was almost twice as low in the treatment group compared with the control at 6–11 h postoperatively, but the differences were not statistically significant.

DISCUSSION

This study suggests that perioperative gabapentin reduces postoperative fentanyl use in patients undergoing TKA;

Table 1. Patient Characteristics

Variable	Treatment group (n = 49)	Control group (n = 46)	P value
Age (yr)	66.8 \pm 7.3	65.9 \pm 8.3	0.557
Female (%)	89.8	89.1	0.917
Body mass index (kg/m ²)	29.4 \pm 4.3	27.9 \pm 3.4	0.069
Duration of anesthesia (h)	2.5 \pm 0.5	2.6 \pm 0.6	0.690
Duration of surgery (h)	1.3 \pm 0.4	1.2 \pm 0.5	0.237
ASA class (%)			0.017*
I	6.1	13.0	
II	73.5	82.6	
III	20.4	4.3	
Right/Left (n)	31/18	27/19	

Values are the mean \pm SD. * $P < 0.05$.

Table 3. Fentanyl Consumption (μg)

	Treatment group (n = 49)	Control group (n = 46)	P value
Fentanyl consumption			
1st day	485.1 \pm 13.5	491.7 \pm 17.5	0.053
2nd day	349.7 \pm 83.2	405.2 \pm 64.1	0.001*
Bolus fentanyl	12.3 \pm 20.7	14.1 \pm 17.6	0.656

Values are the mean \pm SD. *Significant at $P < 0.05$.

Table 2. Pain Measurement

Time period	Mean VAS score at rest			Mean VAS score on movement		
	Treatment group (n = 49)	Control group (n = 46)	P value	Treatment group (n = 49)	Control group (n = 46)	P value
0–5 h	0.00 \pm 0.02	0.02 \pm 0.09	0.173	0.03 \pm 0.10	0.02 \pm 0.09	0.785
6–11 h	0.18 \pm 0.52	0.53 \pm 0.68	0.006	0.24 \pm 0.68	0.78 \pm 0.75	0.001*
12–23 h	0.25 \pm 0.69	0.57 \pm 0.69	0.026	0.32 \pm 0.85	1.03 \pm 1.24	0.001*
24–47 h	0.16 \pm 0.44	0.56 \pm 0.74	0.002*	0.24 \pm 0.50	1.14 \pm 1.27	0.001*
48–72 h	0.08 \pm 0.44	0.26 \pm 0.48	0.059	0.13 \pm 0.50	0.71 \pm 1.15	0.002*
Total (mean)	0.14 \pm 0.37	0.39 \pm 0.40		0.19 \pm 0.46	0.74 \pm 0.71	

Values are the mean \pm SD. *Significant at $P < 0.005$ after Bonferroni's correction.

Table 4. Number of Patients Experiencing Nausea and Vomiting

Time period	Nausea		Vomiting	
	Treatment group (n = 49)	Control group (n = 46)	Treatment group (n = 49)	Control group (n = 46)
0-5 h	10 (14.3%)	7 (8.1%)	5 (15.6%)	3 (11.1%)
6-11 h	17 (24.3%)	33 (38.4%)	16 (50.0%)	15 (55.6%)
12-23 h	19 (27.1%)	19 (22.1%)	6 (18.8%)	6 (22.2%)
24-47 h	15 (21.4%)	18 (20.9%)	4 (12.5%)	2 (7.4%)
48-72 h	9 (12.9%)	9 (10.5%)	1 (3.1%)	1 (3.7%)
Total	70	86	32	27
P value	0.364		0.579	

Values are the number (%) of patients.

however, the difference was not clinically significant. Pain after TKA is due to both surgical stimulation and neurogenic factors. Recent postoperative pain treatment methods include several analgesic drugs with different mechanisms of action [3]. Gabapentin is primarily used as an anticonvulsant, but many studies have demonstrated that it also has antihyperalgesic effects [6-11]. Presurgical treatment with gabapentin may prevent abnormal pain responses such as hyperalgesia and allodynia and it reduced acetic acid-induced visceral nociception in animal studies [13,14]. The mechanism of the antihyperalgesic action may be the result of postsynaptic binding to the α_2 -delta subunits of the voltage-gated calcium channels in the dorsal horn neurons in the spinal cord, causing decreased calcium entry into nerve endings, attenuating postsynaptic excitability, and decreasing the release of neurotransmitters. The decreased calcium influx reduces the release of excitatory amino acids such as glutamate and substance P, leading to a reduction in the hyperexcitability of dorsal horn neurons induced by tissue and nerve damage [15,16].

There is evidence that gabapentin safely reduces the VAS pain score, increases patient satisfaction and decreases postoperative nausea, vomiting and pruritus [6-11,17]. Gabapentin has been used to treat postoperative acute and chronic pain following major lower limb surgery [7,18-21]. However, a recent well-designed study found that the use of gabapentin cannot prevent acute postoperative pain following TKA, and it resulted in increased adverse reactions [12].

Pre-procedural gabapentin treatment is also effective in treating pain during spinal, otolaryngological, gynecological, and endoscopic procedures, and burn wound debridement [9,15,16,22-25]. Some studies suggest that it reduces the stress response that may occur during laryngoscopy and tracheal intubation [26].

In our study, diclofenac sodium, metamizole, and a single-shot femoral block were administered preoperatively. Gabapentin was used as an additional agent in the treatment group. Postoperatively, all patients were given a background infusion of PCA fentanyl. On the first day, the fentanyl consumption was the same in both groups. On the second day, however, the fentanyl consumption was significantly lower in the treatment group. Clinically, however, 50 μ g may not provide a significant difference. This difference may be attributed to the use of multimodal analgesia. Using the VAS, the overall level of pain was low compared with other studies [6-11], although the scores were higher in the control group. This overall low level of pain reported in our Mongolian patients may be an area for further study. In animals, gabapentin increases the effect of diclofenac sodium when these are used together in the subarachnoid space [27]. In our patients, diclofenac sodium 75 mg IM was given 1 h preoperatively and three times a day postoperatively to both groups. This treatment will affect postoperative pain relief. One study reported that gabapentin and morphine have synergistic effects [28].

Studies have used different doses of gabapentin for pre- and postoperative pain management. Some studies suggest starting with a 300-mg dose for acute pain, although a preoperative dose of more than 600 mg was not effective at reducing postoperative pain [29]. We gave gabapentin 600 mg 2 h preoperatively and 300 mg for 3 nights postoperatively. Some studies reported a higher incidence of sedation and somnolence with higher doses, so we opted for 300 mg of gabapentin in the evenings because our patients were not closely monitored at night.

Gabapentinoid drugs have relatively mild side effects, but high doses can cause dizziness, sedation, nausea, loss of balance, lower limb edema, urinary retention, constipation, and

pruritus [11,12,30]. Several studies using gabapentinoids for acute postsurgical pain have reported PONV. In a study using gabapentin for hysterectomy pain, PONV was more common in the control group than in the treatment group. Studies have revealed that gabapentin reduces PONV [8,30]. In our study, there was no significant difference in the incidence of vomiting between the two groups, while nausea was 50% less frequent in the treatment group 6–11 h postoperatively, which is consistent with other studies [8,21]. One of our patients experienced higher sedation on the 2nd and 3rd postoperative days; however, no serious problem was identified on brain computed tomography. The PCA fentanyl and gabapentin were discontinued in this patient, who was removed from the analysis. We did not observe any other side effects of gabapentin, such as loss of balance, lower limb edema, and pruritus. In our hospital setting, all TKA patients had lower limb edema for 3–4 days, which was mainly due to fluid infusion to manage hypotension, the tourniquet, and the major surgery leading to disruption of the lymphatics.

There are several limitations to our study. The distribution by ASA class in the two groups was relatively uneven. There is also increasing debate in the arthroplasty literature on the value of a physiotherapy measure of functional outcome. Therefore, future research should incorporate functional outcome measures, both self-reported and rehabilitation-based, to monitor recovery following TKA. One reason that we wished to explore the value of gabapentin in our country (with its irregular supply chain, limited access to PCA machines, and limited skills in peripheral nerve blocks) was to see if the medication would be valuable under our conditions. We now plan to study the use of gabapentin without the use of nerve blocks or PCA fentanyl. While this might be seen as providing a less satisfactory level of multimodal analgesia, it is standard practice in some areas; also, the simple addition of oral gabapentin may improve outcomes in these settings.

In conclusion, perioperative gabapentin for TKA does not reduce postoperative pain or lead to a clinically significant reduction in fentanyl use in the context of multimodal analgesia.

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