Effect of pre-emptive gabapentin on postoperative pain following lower extremity orthopaedic surgery under spinal anaesthesia

Panah Khahi M, Yaghooti A A, Marashi S H, Nadjafi A

ABSTRACT

Introduction: Gabapentin has demonstrated efficacy in clinical trials as a pre-emptive analgesic and in acute postoperative pain management. However, our experience with the drug is still limited. The present study was conducted in order to evaluate the effect of gabapentin on reduction of postoperative pain in the first 24 hours after internal fixation of the tibia under spinal anaesthesia.

Methods: In a double-blind, randomised controlled clinical trial, 64 American Society of Anesthesiologists Class I or II patients, who underwent internal fixation of the tibia, were administered 300 mg of gabapentin or a placebo two hours before surgery. The postoperative pain was assessed using Visual Analogue Scale two, 12 and 24 hours after surgery. The time from the end of surgery until the first bolus dose of morphine on demand (pain score > 4) and the total morphine requirement were recorded. Patients were also asked about the possible side effects of gabapentin.

Results: The pain score was significantly lower in the gabapentin group at two hours post surgery (p-value is 0.004), while the scores at 12 and 24 hours post surgery were not significantly different between the two groups. No side effect of gabapentin was observed.

Conclusion: Pre-emptive use of gabapentin 300 mg orally significantly decreases postoperative pain two hours after surgery.

Keywords: gabapentin, morphine demand, orthopaedic surgery, postoperative pain, pre-emptive analgesia

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INTRODUCTION

Gabapentin is an anticonvulsant agent that is structurally related to gamma-aminobutyric acid (GABA). It has an effective antinociceptive or antihyperalgesic action for the prevention of postoperative pain in addition to being an anticonvulsant, based on experimental models of neuropathic pain and inflammatory hyperalgesia. Gabapentin was shown to reduce sensitisation of dorsal horn neurons of the spinal cord or brain.[1-7] The mechanism of action of gabapentin is likely mediated by binding to the 21 subunits of the presynaptic voltage-gated calcium channels, which are upregulated in the dorsal root ganglia and spinal cord after surgical trauma.[8] Other hypothesised mechanisms are increased GABA synthesis in the brain, reduction of monoamine neurotransmitters and increase in serotonin concentration of the blood.[9]

In recent years, gabapentin has been introduced as an adjunct in the multimodal approach to managing acute postoperative pain. However, before it could be recommended for routine clinical use, more studies on dosing, efficacy, adverse effect profile, ideal timing and duration of treatment to reduce acute postoperative pain and to prevent chronic postoperative pain are required.[10] Although gabapentin has demonstrated analgesic effects in clinical trials as a pre-emptive analgesic and in acute postoperative pain management, our experience with the drug is still limited.[11-13] Antinociceptive treatment started before surgery (pre-emptive analgesia) is more effective in reducing postoperative pain than if started in early postoperative period.

The bioavailability of gabapentin varies inversely with its dose. The peak plasma level is achieved three hours after ingestion of a single 300 mg capsule. Gabapentin is eliminated unchanged in the urine, with an elimination half-life of 5–9 hours.[8] Thus far, no investigation has been done on the pre-emptive use of gabapentin in orthopaedic surgery under spinal anaesthesia. Therefore, the present study was designed to evaluate the effect of pre-emptive use of gabapentin

300 mg orally on the reduction of postoperative pain and morphine consumption in the first 24 hours after internal fixation of the tibia under spinal anaesthesia.

METHODS

In this double-blind, randomised controlled clinical trial, 64 American Society of Anesthesiologists (ASA) Class I or II patients undergoing internal fixation of the tibia were recruited. Inclusion criteria were ASA Class I or II, 16–70 years of age and an estimated surgery duration of 120–150 minutes. Patients with known sensitivity to gabapentin, a history of seizure, a positive history of gabapentin consumption, psychiatric disorders, drug abuse, known liver or renal disease, chronic pain syndrome, intake of analgesic drugs during the last 24 hours, known sensitivity to bupivacaine as well as those who did not consent to spinal anaesthesia were excluded from the study.

Only patients who provided written informed consent were included in the study. The patients were randomly assigned to receive gabapentin or a placebo. Randomisation was performed centrally using a table of random numbers. Patients in the treatment group were given 300 mg gabapentin capsule (Sobhan Co, Tehran, Iran) and those in the other group took a placebo 120 minutes before surgery. Gabapentin and the placebo were identical in appearance. All patients as well as trial nurses were blinded to the study-group assignment.

After placement of standard non-invasive monitoring devices, a midline lumbar puncture was performed using a 25-gauge pencil-type needle at the L3–4 level with the patient in a sitting position. Spinal injection of 3 ml (15 mg) isobaric bupivacaine (0.5%) was administered to all patients, after which they were immediately turned to the supine position until the end of the operation. The surgery was started after complete sensorimotor block at the level of T8–T10. The patients were sedated with 1–2 mg of midazolam.

During the pre-anaesthetic round, the patients were trained in the use of the pain score (0 for no pain and 10 for extremely intense pain. During anaesthesia, continuous electrocardiography, heart rate, pulse oximetery and non-invasive arterial pressure were monitored and recorded.

After the surgery, an anaesthesiologist who was blinded to the patient groups recorded the pain score at two, 12 and 24 hours after surgery, and also asked the patients to evaluate the possible side-effects of the drug (e.g. somnolence, nystagmus, tremor, diplopia, nausea). The time from the end of the surgery until the first bolus of morphine administered on demand (pain score > 4) and the total morphine requirement in the first 24 hours were recorded.

Table I. Baseline characteristics.

Variable	Mean ± SD		p-value
	Gabapentin	Placebo	
Age (yrs)	32.28 ± 13.7	32.7 ± 13.6	0.863
Male:female ratio	28:4	25:7	0.509
ASA Class I:II ratio	25:7	20:12	0.171
Duration to first dose of MS (hrs)	4 ± 1.96	3.17 ± 1.85	0.11
Required dose of MS (mg)	5.25 ± 2.65	5.6 ± 2.29	0.529

SD: standard deviation; MS: morphine sulphate

Table II. Pain scores.

Group	Mean pain score ± SD		
	2 hr	12 hr	24 hr
Gabapentin	3.31 ± 1.53	7.91 ± 1.9	2.81 ± 1.59
Placebo	4.53 ± 1.83	7.69 ± 2.38	2.88 ± 1.59
p-value*	0.004	0.984	0.607

* Using non-parametric Mann-Whitney test.

All data underwent Kolmogorov-Smirnov Z test to assess distribution normality. The analyses were performed using chi-square test, independent *t*-test and Mann-Whitney test with intention-to-treat method. A p-value < 0.05 was considered statistically significant. Data was analysed using the Statistical Package for the Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA). Quantitative data were presented as mean ± standard deviation.

RESULTS

The gabapentin group included 32 subjects with mean age 32.28 ± 13.7 years and male to female ratio of 28:4. The placebo group consisted of 32 patients with mean age 32.7 ± 13.6 years and male to female ratio of 25:7. The two groups did not have any significant difference in baseline characteristics (Table I). All recruited patients completed the study and underwent analysis (Fig. 1).

The pain score was significantly lower in patients belonging to the gabapentin group at the second hour after surgery (3.31 ± 1.53 vs. 4.53 ± 1.83, p-value = 0.004). Pain score at other times did not show significant difference between the two groups (Table II). No side effect was observed in the gabapentin group.

DISCUSSION

The present study was a randomised controlled clinical trial to evaluate the effect of gabapentin on pain reduction

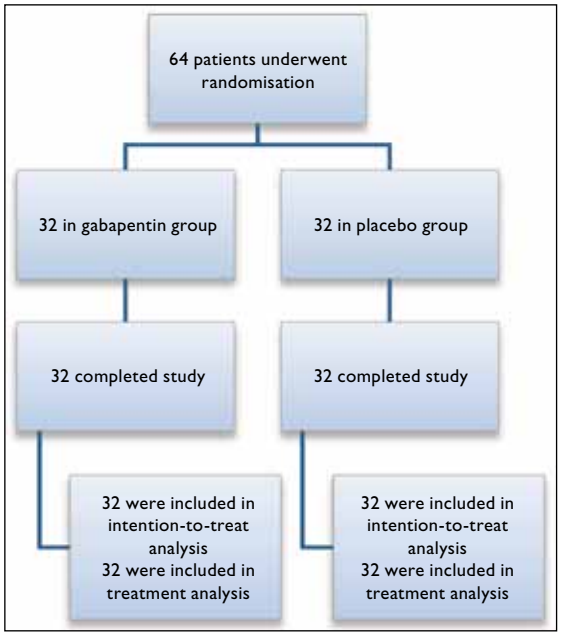

Fig. 1 Enrollment and outcomes.

after internal fixation of the tibia under spinal anaesthesia. When gabapentin was administered two hours before anaesthesia, pain reduction was noted at the second hour after surgery; however, it did not show any effect on the pain at the 12th and 24th hour after surgery in comparison with the placebo. Also, the patients' first demand and dose requirement of morphine did not decline with the use of gabapentin. No significant adverse effects were seen with a single dose of gabapentin. Previous studies have shown that gabapentin has some antinociceptive or antihyperalgesic action for the prevention of postoperative pain after general anaesthesia, monitored anaesthesia care and other anaesthetic methods, but no study has investigated the effect of this drug on spinal anaesthesia.[1-7,15,16]

Considering that the time of peak concentration of gabapentin is three hours and its half-life is 5–9 hours after ingestion of the 300-mg capsule, the findings of the present study may be acceptable. The result of the first assessment of post-surgical pain score was compatible with the time of peak concentration of gabapentin, and the second assessment was conducted out of the half-life of this drug. Although insignificant, the demand for morphine was delayed in the gabapentin group and the total dose requirement of morphine was lower than that of the placebo group, which could be due to the short effect of a single dose of gabapentin. In other studies, gabapentin was administered as a single dose of 300–1,200 mg one to two hours before surgery.

In a study by Montazeri et al, gabapentin 300 mg administered two hours before orthopaedic surgery significantly reduced the pain score and morphine requirement after general anaesthesia.[9] Other studies have reported gabapentin as an effective medication for acute pain, resulting in a lower morphine requirement after surgery performed with intravenous regional anaesthesia for hand microsurgery (1,200 mg single dose, one hour before surgery)[17] or with general anaesthesia for lumbar discoidectomy (300 mg single dose, two hours before surgery)[18] and laparoscopic cholecystectomy (300 mg single dose, two hours before surgery).[19] These results are in contrast with studies that reported no difference in acute post-surgical pain after interscalene brachial plexus block for arthroscopy (800 mg single dose, two hours before surgery)[15] or general anaesthesia for thyroidectomy (1,200 mg single dose in combination with superficial cervical plexus block, two hours before surgery). Further investigations suggested that a single-dose gabapentin 600 mg was the optimal dose, independent of, before- or after-surgery consumption.[20,21]

In conclusion, considering the previous findings and the results of the present study, gabapentin should be consumed in sufficient dose to have effective blood concentration. This could be an effective drug to control acute post-surgical pain after selective anaesthesia.

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