Perioperative administration of gabapentin 1,200 mg day^{-1} and pregabalin 300 mg day^{-1} for pain following lumbar laminectomy and discectomy: a randomised, double-blinded, placebo-controlled study

Ozgencil E, Yalcin S, Tuna H, Yorukoglu D, Kecik Y

ABSTRACT

Introduction: Gabapentin and pregabalin have been compared in studies conducted on management of neuropathic and postoperative pain. In neuropathic pain studies, the analgesic effects of the two drugs were compared, and pregabalin has been found to be more potent. However, in postoperative pain studies, the effects of each drug were examined separately. This study compared the analgesic effects of pregabalin (300 mg day^{-1}), gabapentin (1,200 mg day^{-1}) and a placebo in managing postoperative pain following laminectomy and discectomy.

Methods: 90 patients were randomly assigned to three groups (pregabalin, gabapentin and placebo) of 30 patients each. Pregabalin 150 mg, gabapentin 600 mg and a placebo were administered every 12 hours, two times pre- and post surgery. Study data collected included morphine consumption, Visual Analogue Scale records, preoperative anxiety, patient satisfaction, adverse effects and observation notes.

Results: In the gabapentin and pregabalin groups, overall morphine consumption, preoperative anxiety, pruritus, postoperative shivering were significantly lower (p-value less than 0.05 for all), and patient satisfaction was significantly higher than those in the placebo group (p-value less than 0.05).

Conclusion: This study showed that both pregabalin 300 mg day^{-1} and gabapentin 1,200 mg day^{-1} have more analgesic, anxiolytic and opioid-sparing effects, higher patient satisfaction and are more effective for preventing postoperative shivering than the placebo following lumbar laminectomy and discectomy. The findings revealed that pregabalin 300 mg day^{-1} had equivalent analgesic, adverse and opioid-sparing effects and patient satisfaction as gabapentin 1,200 mg day^{-1}.

Keywords: discectomy, gabapentin, laminectomy, postoperative pain, pregabalin

Singapore Med J 2011; 52(12): 883-889

Department of Anaesthesiology and Reanimation, Medical Faculty of Ankara University, Ibni Sina Hastanesi, Sihhiye 06100, Ankara, Turkey

Ozgencil E, MD Specialist

Yorukoglu D, MD Professor

Kecik Y, MD Professor

Department of Neurosurgery

Tuna H, MD Associate Professor

Department of Anaesthesiology and Reanimation, Medical Faculty of Harran University, Araştırma Hastanesi, Sanliurfa 63100, Turkey

Yalcin S, MD Assistant Professor

Correspondence to: Dr Enver Ozgencil Tel: (90) 31 2595 2393 Fax: (90) 31 2311 5057 Email: geno6700@hotmail.com

INTRODUCTION

Approximately 80% of patients undergoing surgical procedures experience postoperative pain.[1] Although there are many analgesic drugs available for postoperative pain, many patients still find them to be suboptimal for controlling pain. Opioids are the mainstay for treating moderate to severe postoperative pain, but their use is limited due to adverse effects such as nausea, vomiting, excessive sedation, respiratory depression, pruritis and urinary retention.[2] Currently, the popularity of multimodal analgesia, the use of two or more analgesics and modalities that work by different mechanisms to improve analgesia and reduce the severity of adverse effects, is rising steadily. One of these multimodal analgesia techniques is the administration of anticonvulsant agents such as gabapentin and pregabalin.

Pregabalin and its predecessor, gabapentin, are analogues of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). They have anticonvulsant, antihyperalgesic and anxiolytic effects, and both bind to the alpha 2-delta (α2-δ) subunit of the presynaptic, voltage-gated calcium channels that are widely distributed throughout the peripheral and central

nervous system. The probable mechanism of action of pregabalin/gabapentin is to reduce the release of several excitatory neurotransmitters (e.g. glutamate, substance P, calcitonin, noradrenaline, gene-related peptid) by inhibiting calcium influx via the calcium channels.[3-6]

The pharmacological activity of pregabalin is similar to, but not identical with, that of gabapentin.[7] Although it is structurally similar to gabapentin, pregabalin has greater analgesic efficacy in rodent models of neurophatic pain, diabetic peripheral neuropathy[8] and postherpetic neuralgia,[9] and also has lower inter-subject variability. Pregabalin is pharmacologically superior to gabapentin due to its higher bioavailability (90% vs. 33%–66%), more rapid absorption (peak plasma level: 1 hr vs. 3–4 hrs) and linear increase in plasma concentration when its dose is increased. Lower doses of pregabalin than that of gabapentin (2–4 fold lower doses) have a similar analgesic effect on neuropathic pain, which makes pregabalin more advantageous in terms of the side effects from dosage.[10-13] Pregabalin has also shown better analgesic efficacy than gabapentin in diabetic peripheral neuropathy and postherpetic neuralgia over a 12-week period.[14]

In the last decade, gabapentin, and more recently pregabalin, have been used in many prospective randomised trials that evaluated their effectiveness in reducing postoperative pain. In postoperative pain studies, the two drugs have been compared to a placebo in separate designs, but they have never been studied simultaneously in one design. However, in neuropathic pain studies, gabapentin has previously been compared to pregabalin. Hence, this study aimed to examine whether pregabalin has a similar analgesic efficacy to gabapentin when its dose was four times lower than that of gabapentin.

METHODS

After approval from the local ethics committee, written informed consent was obtained from the patients who were scheduled to undergo elective decompressive lumbar laminectomy and discectomy. Patients with the following characteristics were excluded from the study: age < 18 years; age > 70 years; pregnant; allergic and/or contraindicated to one or more of the drugs studied; American Society of Anesthesiologists (ASA) score III and above; having drug and/or alcohol addiction, renal failure, diabetes mellitus or epilepsy; and currently using opioids for chronic pain and/or any of the drugs studied. A total of 90 patients were included in the study. Patients were randomly assigned to three groups using a computer-generated randomisation schedule.

The patients, anaesthesiologists and surgeons were blinded to the drug administered. A physician, who was not a member of the anaesthesia or surgical team, recorded the study data. Patients in Group 1 (placebo, n = 30) received 'placebo 14' two hours prior to the operation, and ten and 22 hours after the operation (over two days). Patients in Group 2 (GABA, n = 30) received gabapentin 600 mg at the same time intervals as Group 1 patients (1,200 mg day^{-1}). Patients in Group 3 (PGABA, n = 30) received pregabalin 150 mg with the same schedule (300 mg day^{-1}).

Preoperative anxiety was scored on a seven-point scale (1 = relaxed, 2 = apprehension, 3 = mild anxiety, 4 = moderate anxiety, 5 = manifest anxiety, 6 = severe anxiety, 7 = very severe anxiety). General anaesthesia was induced with thiopental sodium (4 mg/kg), remifentanil (1 μg/kg), and rocuronium (0.6 mg/kg), and maintained with desflurane and 70% N_2O in O_2. Desflurane concentration was adjusted to maintain adequate depth of anaesthesia. Remifentanil infusion (0.15–0.30 μg kg^{-1} min^{-1}) was continued during the operation. No other analgesic was administered during the surgery. After tracheal extubation, the patients were transferred to the post anaesthesia care unit (PACU). Intravenous lornoxicam 8 mg was used as a rescue analgesic, but none of the patients needed it.

The patients were connected to a morphine patient-controlled analgesia (PCA) pump on arrival at the PACU. The PCA pump was set to deliver a loading dose of 2.5 mg and an incremental dose of 2.5 mg at a lockout interval of eight minutes and a four-hour limit of 50 mg. The incremental dose was increased to 3 mg, the lock-out interval decreased to six minutes and the four-hour limit increased to 60 mg, whenever the analgesia was inadequate after one hour. Before the operation, the patients were trained on how to use the PCA pump. They were also taught how to express the level of pain they experienced using an 11-point Visual Analogue Scale (VAS), with 0 indicating no pain and 10 indicating the worst possible pain. Anxiety scores, vital signs, pain scores, Numeric Sedation Scores (NSS; 1 = completely awake, 2 = awake but drowsy, 3 = asleep but responsive to verbal commands, 4 = asleep but responsive to tactile stimulus, 5 = asleep and not responsive to any stimuli), morphine consumption and adverse effects such as nausea, vomiting, pruritus, urinary retention, somnolance, dizziness, vision abnormalities (double or blurred) and headache were recorded.

Except for the anxiety scores that were recorded only once before the operation, all postoperative variables were recorded on the 1st, 2nd, 4th, 6th, 12th and 24th

Table I. Demographic data.

Demographic	Placebo (n = 30)	Gabapentin (n = 30)	Pregabalin (n = 30)
Mean age ± SD (yr)	48.6 ± 6.5	50.6 ± 9.1	51.9 ± 7.1
Mean weight ± SD (kg)	74.3 ± 8.6	71 ± 9.7	69.2 ± 7.2
Gender			
Male	13 (43.3)	15 (50)	12 (40)
Female	17 (56.7)	15 (50)	18 (60)
Mean duration of surgery ± SD (hr)	2.24 ± 0.33	2.32 ± 0.45	2.10 ± 0.25

Data is presented as mean ± SD or no. of patients (%)

Table II. Morphine consumption and patient satisfaction with anaesthesia and pain management.

	Placebo (n = 30)	Gabapentin (n = 30)	Pregabalin (n = 30)
Morphine consumption (mg kg^{-1})			
1 hr post surgery	4.47 ± 2.27	4.87 ± 2.81	4.33 ± 2.63
2 hr post surgery	10 ± 3.28	8.67 ± 4.67	8.27 ± 4.51
4 hr post surgery	17.07 ± 4.89	13.27 ± 6.46	13 ± 7.23
6 hr post surgery	23.87 ± 7.14	19.27 ± 8.31	16.69 ± 8.75†
12 hr post surgery	30.93 ± 8.7	24.33 ± 8.91†	21.6 ± 8.9*
24 hr post surgery	37.33 ± 9.5	29.47 ± 9.64†	26.33 ± 9.41*
Total (24 hrs)	0.51 ± 0.14	0.41 ± 0.13†	0.36 ± 0.13*
Satisfaction with pain medication			
Good	3 (10)	10 (33.3)*	11 (36.7)*
Excellent	0 (0)	5 (16.7)*	8 (26.7)*

Data is presented as morphine consumption: mean ± SD, satisfaction with pain medication: no. of patients (%)
*$p < 0.001$ vs. placebo; †$p < 0.05$ vs. placebo

hour post operation (six times altogether). 24 hours post operation, the patient's satisfaction with his pain and anaesthetic management (scored on a 5-point scale; 0 = poor, 1 = fair average, 2 = moderate, 3 = good and 4 = excellent) during the pre- and postoperative periods was recorded. All other postoperative signs and patients' complaints were recorded in the observation form under the 'others' category by an external investigator who observed the patients after the operation and recorded any complaints or signs noted.

The minimum sample size required for the study was computed based on the primary outcome variable, i.e. consumption of morphine. Power analysis was performed using G*Power version 3.0.10 (Dusseldorf University, Dusseldorf, Germany). In order to detect a 35% difference in the consumption of morphine among the three groups with a standard deviation of 20 (σ) and a power of 83% (1-β) at 5% significance level (α), the power analysis recommended approximately 90 patients (30 per group) as the total sample size.

The patients' age, weight, anxiety and VAS scores, morphine consumption and duration of operation were analysed using one-way analysis of variance (ANOVA). Post-hoc analyses using Tukey adjustment were performed. The NSS data, observed adverse effects, patients' gender and their satisfaction scores were analysed using χ^2 test. The postoperative observation data recorded under the 'others' category was coded. Among the codes generated were 'shivering' (0 = no shivering observed, 1 = shivering observed), 'tenseness' (0 = no tenseness reported, 1 = tenseness reported) and 'lack of appetite' (0 = no lack of appetite reported, 1 = lack of appetite reported). Observed variables were analysed using χ^2 test. The statistical analyses were computed using the Statistical Package for the Social Sciences Windows version 15.0 (SPSS Inc, Chicago, IL, USA).

RESULTS

Patients' demographics and duration of surgery did not differ among the groups (Table I). The amount of morphine consumed was similar among the three groups at the 1st, 2nd, and 4th hour post operation (Table II). At the 6th postoperative hour, morphine consumption level was significantly lower in the pregabalin group compared to the placebo group ($p < 0.003$; ANOVA, post-hoc analysis using Tukey adjustment), although it was similar between the placebo and gabapentin groups. Morphine consumption at the 12th and 24th hour was significantly lower in the gabapentin group (respectively at $p < 0.013$, $p < 0.005$; ANOVA, post-hoc analysis using Tukey adjustment) and pregabalin group (respectively at $p < 0.001$, $p < 0.001$; ANOVA, post-hoc analysis using Tukey adjustment) compared to the placebo group.

Table III. Data on Visual Analogue Scale (VAS) and anxiety scores.

	Placebo (n = 30)	Gabapentin (n = 30)	Pregabalin (n = 30)
Visual Analogue Scale			
1 hr post surgery	5.7 ± 1.08 (5.3–6.1)	4.66 ± 1.18 (4.2–5.1)†	4.46 ± 1.25 (3.9–4.9)*
2 hr post surgery	5.36 ± 1.03 (4.9–5.7)	3.53 ± 0.89 (3.2–3.8)*	3.5 ± 1.13 (3–3.9)*
4 hr post surgery	4.23 ± 1.33 (3.7–4.7)	2.73 ± 0.9 (3.2–3.8)*	2.83 ± 1.11 (3.1–3.9)*
6 hr post surgery	3.33 ± 1.09 (2.9–3.7)	2.4 ± 0.67 (2.1–2.6)*	2.36 ± 0.92 (2–2.7)*
12 hr post surgery	2 ± 0.74 (1.7–2.8)	1.56 ± 0.62 (1.3–1.8)	1.56 ± 0.97 (1.2–1.9)
24 hr post surgery	1.5 ± 0.77 (1.2–1.8)	1.1 ± 0.48 (0.9–1.3)	1.1 ± 1.18 (0.6–1.5)
Anxiety score	2 ± 0.64 (1.76–2.24)	1.6 ± 0.62 (1.37–1.83)†	1.57 ± 0.67 (1.31–1.82)†

Data is presented as mean ± SD (95% confidence interval)
*p < 0.001 vs. placebo; †p < 0.05 vs. placebo

Table IV. Data on numeric sedation score (NSS), adverse effects and shivering.

	Placebo (n = 30)	Gabapentin (n = 30)	Pregabalin (n = 30)
NSS			
1 hr post surgery	1.56 ± 0.67; 1 (1–3)	2.2 ± 0.66; 2 (1–3)*	2 ± 0.74; 2 (1–3)†
2 hr post surgery	1.63 ± 0.66; 2 (1–3)	2.23 ± 0.56; 2 (1–3)†	2.06 ± 0.69; 2 (1–3)†
4 hr post surgery	1.6 ± 0.49; 2 (1–2)	2.1 ± 0.6; 2 (1–3)†	1.96 ± 0.49; 2 (1–3)†
6 hr post surgery	1.66 ± 0.47; 2 (1–2)	2.03 ± 0.61; 2 (1–3)†	2 ± 0.26; 2 (1–3)†
12 hr post surgery	2.06 ± 0.52; 2 (1–3)	2.1 ± 0.48; 2 (1–3)	1.96 ± 0.18; 2 (1–2)
24 hr post surgery	2.16 ± 0.37; 2 (2–3)	2.16 ± 0.46; 2 (1–3)	2.03 ± 0.18; 2 (2–3)
Adverse effects			
Nausea	7 (23.3)	8 (26.7)	5 (16.7)
Vomiting	5 (16.7)	3 (10)	3 (10)
Dizziness	6 (20)	9 (30)	8 (26.7)
Somnolance	5 (16.7)	8 (26.7)	7 (23.3)
Headache	1 (3.3)	5 (16.7)	2 (6.7)
Blurred vision	0 (0)	0 (0)	2 (6.7)
Urine retention	9 (30)	4 (13.3)	5 (16.7)
Pruritus	14 (46.7)	5 (16.7)†	4 (13.3)†
Shivering	8 (26.7)	2 (6.7)†	1 (3.3)†

Data is presented as NSS: mean ± SD; median (range), adverse effects and shivering: no. of patients (%)
*p < 0.001 vs. placebo; †p < 0.05 vs. placebo.

Also, the overall morphine consumption per kg was significantly lower in both the gabapentin and pregabalin groups compared to the placebo group (respectively at $p < 0.026$ and $p < 0.001$; ANOVA, post-hoc analysis using Tukey adjustment). Although morphine consumption was lower in the pregabalin group compared to the gabapentin group, it was not statistically significant during the entire 24-hour postoperative period. Overall patient satisfaction with pain management was higher in the gabapentin ($p < 0.001$; χ^2 test) and pregabalin ($p < 0.001$; χ^2 test) groups compared to the placebo group (Table II). Patients in the gabapentin and pregabalin groups expressed similar levels of satisfaction with the anaesthesia and pain management.

The VAS scores recorded in the 1st, 2nd, 4th and 6th postoperative hours were significantly lower in the gabapentin ($p < 0.003$, $p < 0.001$, $p < 0.001$ and $p < 0.001$ respectively; ANOVA, post-hoc analysis using Tukey adjustment) and pregabalin ($p < 0.001$, $p < 0.001$, $p < 0.001$ and $p < 0.001$ respectively; ANOVA, post-hoc analysis using Tukey adjustment) groups compared to the placebo group. The VAS scores in the 12th and 24th postoperative hours were similar among the three study groups (Table III). Patients' anxiety scores were significantly lower in the gabapentin and pregabalin groups compared to the placebo group ($p < 0.049$ and $p < 0.030$ respectively; ANOVA, post-hoc analysis using Tukey adjustment) (Table III).

In the 1st, 2nd, 4th and 6th hour, the NSS was higher in the gabapentin group (respectively, $p < 0.001$, $p < 0.002$, $p < 0.004$, $p < 0.029$; $\chi 2$ test) and the pregabalin group (respectively, $p < 0.026$, $p < 0.020$, $p < 0.028$, $p < 0.036$; χ^2 test) compared to the placebo group. There was no difference in the NSS in the 12th and 24th postoperative hours, and no difference between the gabapentin and pregabalin groups during the entire postoperative day (Table IV). Except for pruritus, the adverse effects observed were similar among the study groups. The incidence of pruritus was lower in both the gabapentin and pregabalin groups compared to the placebo group

(respectively $p < 0.018$ and $p < 0.007$; χ^2 test).

Analysis of the codes generated under the 'others' category showed that only postoperative 'shivering' was significantly different among the groups. Reported feelings of 'tenseness' and 'lack of appetite' were not found to be significantly different among the patients in all three groups. The incidence of postoperative shivering was 26.7% (n = 8) in the placebo group, 6.7% (n = 2) in the gabapentin group and 3.3% (n = 1) in the pregabalin group. Only significant differences were observed between the gabapentin and placebo groups ($p < 0.038$, χ^2 test), and between the pregabalin and placebo groups ($p < 0.011$, χ^2 test).

DISCUSSION

The present study showed that the analgesic efficacy provided by pregabalin 300 mg day^{-1} was equivalent to that provided by gabapentin 1,200 mg day^{-1} for postoperative pain following lumbar laminectomy and discectomy. The adverse effects of the two drugs observed in this study were also similar.

The use of a lower dose of pregabalin over gabapentin in neuropathic pain has previously been reported.[9-14] This is not surprising, as pregabalin has a higher bioavailability (90%), is more rapidly absorbed (peak at one hour) than gabapentin (33%–66% bioavailability and peak at 3–4 hours) and requires lower dosages. The plasma concentration of pregabalin increases linearly with increasing dose, whereas that of gabapentin increases non-linearly with increasing dose.[3,15,16] Hence, pregabalin is known to be pharmacokinetically superior to gabapentin. However, lower doses of pregabalin did not provide better patient satisfaction and fewer adverse effects than gabapentin. A different dose ratio of gabapentin and pregabalin from the one used in this study (300 mg day^{-1} vs. 1,200 mg day^{-1}) may result in different outcomes. For example, doses of 400 mg day^{-1} pregabalin vs. 1,600 mg day^{-1} gabapentin may reveal differences in analgesic efficacies and adverse effects.

During the first six postoperative hours (as the data collected in the 1st, 2nd, 4th and 6th hour), patients in both the pregabalin and gabapentin groups reported less pain than patients in the placebo group, whereas in the 12th and the 24th postoperative hours, the reported pain scores did not differ among the three groups. This could be due to higher consumption of morphine in the placebo group after the 6th hour compared to the other two groups. The decreasing VAS scores reported could also be associated with the amount of morphine consumption in the placebo group. Cumulative morphine consumption was higher in the placebo group at the 12th and 24th hour. Patients suffering from pain in the placebo group used PCA more frequently in order to achieve the same VAS scores as patients in the pregabaline and gabapentin groups. Over the entire 24-hour postoperative period, the total morphine consumption in the pregabalin (0.36 mg kg^{-1}) and gabapentin (0.41 mg kg^{-1}) groups was lower than that in the placebo group (0.51 mg kg^{-1}). These findings support the observation that gabapentin (1,200 mg day^{-1}) and pregabalin (300 mg day^{-1}) have better analgesic effects than a placebo.

In the literature, the anxiolytic effects of gabapentinoids on panic disorder and social phobia have been reported.[1,18] Gabapentin has been found to possess anxiolytic effects during perioperative knee surgery.[19] In the present study, this anxiolytic effect was observed in both pregabalin and gabapentin.

Studies conducted on gabapentinoids in various surgical procedures reported an opioid-sparing effect of 30%–62%.[20-26] In the present study, the opioid-sparing effects were lower than those previously reported (gabapentin 21.1% and pregabalin 29.5%), both in comparison to the placebo. As opioid consumption decreased, none of the opioid-related adverse effects, except for pruritus, was significantly decreased. The incidence of pruritus in the pregabalin (13.3%) and gabapentin (16.7%) group was significantly lower than that in the placebo group (46.7%). In an earlier study, the opioid-sparing effect of pregabalin, which reduces the occurrence of pruritus, was observed with a dose of 600 mg day^{-1} pregabalin,[25] whereas we observed a decrease in the incidence of pruritus even at a dose of 300 mg day^{-1}.

In Jokela et al's study,[25] patients reported dizziness and blurred vision, but those who were on 600 mg day^{-1} pregabalin did not experience any severe symptoms. Although more patients in the pregabalin and gabapentin groups reported dizziness and somnolence, the differences were not statistically significant. Again, this may be due to the increased consumption of morphine in the placebo group compared to other two groups, which might have led to an increase in dizziness and somnolence. In our study, we observed blurred vision in two patients from the pregabalin group.

The sedation levels (in the first six hours) in the pregabalin and gabapentin groups were significantly higher than those in the placebo group. In the 12th and 24th hours, no difference was observed in the sedation levels. Gabapentin and pregabalin have sedative effects, but morphine as an opioid also has a sedative effect, and this may account for why there was no difference in the sedation scores during the last six hours. This finding

suggests that both pregabalin and gabapentin can raise the sedation levels marginally.[27-33] Although overall patient satisfaction in the gabapentin and pregabalin groups were higher than that in the placebo group, there was no difference between the two groups.

The optimal dosages of the two drugs for postoperative pain are still controversial. In postoperative pain studies, gabapentin doses ranged from 300 mg to 1,200 mg, and those for pregabalin ranged from 50 mg to 300 mg.[28,29] Hence, more comprehensive studies on the optimal dosages of these two drugs for postoperative pain are required. Burke et al[31] found that perioperative pregabalin administration was associated with lesser pain intensity and improved functional outcome three months after lumbar discectomy. Importantly, patients in this same study who received perioperative pregabalin (300 mg at 90 minutes preoperatively and 150 mg at 12 hours and 24 hours postoperatively) had better pain, functional and quality of life outcomes at three months post lumbar discectomy than those who received a placebo, and perioperative pregabalin increased the pain perception threshold in the lower limbs at 24 hours postoperatively.[31] These findings are consistent with those of Jokela et al[25] and Hill et al,[27] who found that perioperative pregabalin had a beneficial effect on postoperative pain scores and analgesic requirements after dental and gynaecological surgery. However, these two studies did not evaluate pain outcomes after 24 hours postoperatively.

Although postoperative shivering was not part of our original study design, it was apparent in the course of the study that incidence of shivering differed among the groups. Patients in the placebo group were found to experience more postoperative shivering than those in the pregabalin and gabapentin groups.

Postoperative shivering is physiologically stressful and unpleasant, and occurs in 6.3%–66% of patients recovering from general anaesthesia.[34] It is classified as thermoregulated and non-thermoregulated shivering. The origin of postoperative shivering is unclear, yet various mechanisms explaining its cause have been proposed.[35] Among the proposed mechanisms are thermoregulatory response to hypothermia, muscle hyperactivity, inhibited spinal reflex, postoperative pain, decreased sympathetic activity, pyrogen release, adrenal suppression and respiratory alkalosis.[36]

Postoperative shivering can cause serious complications, especially for patients who have coronary artery disease and those who are vulnerable to increased intracranial pressure. To prevent postoperative shivering, rewarming of the patient or agents such as pethidin, sufentanil, alfentanil and ketamine can be used.[36-39] The anticonvulsive, anxiolytic and analgesic effects of gabapentinoids may partly reduce the incidence of shivering. However, in the present study, we are unable to explain fully the mechanisms of gabapentionids and the observed postoperative shivering in our patients. As we had not planned on collecting data on postoperative shivering initially, we only recorded shivering as observed vs. not observed. Other variables, including the type, duration and timing of shivering, could be recorded and investigated in future studies that focus on the effects of gabapentinoids on shivering.

In summary, our study findings revealed that in postoperative pain management, gabapentin and pregabalin are the preferred alternatives in multimodal analgesia. Pregabalin 300 mg day^{-1} and gabapentin 1,200 mg day^{-1} exhibited equivalent analgesic, opioid-sparing and adverse effects as well as patient satisfaction. Similar to other neuropathic pain management studies, lower doses of pregabalin were as effective as gabapentin in controlling postoperative pain. Regardless of their dosages, the adverse effects of both drugs were found to be similar. However, a different dose ratio may result in dissimilar adverse effects. Of note is the finding that the incidence of shivering differed among the groups. This has led to plans on designing a protocol investigating the impact of gabapentinoids on postoperative shivering.

ACKNOWLEDGEMENTS

The authors would like to acknowledge the assistance provided by Dr Ayhan Atar, Dr Mevci Ozdemir, Dr Cem Sen and Dr Yesim Ates for this article.

REFERENCES

1. Apfelbaum JL, Chen C, Mehta SS, Gan TJ. Postoperative pain experience: results from a nationale survey suggest postoperative pain continues to be undermanaged. Anesth Analg 2003; 97:534-40.
2. Dolin SJ, Cashman JN. Tolerability of acute postoperative pain management: nausea, vomiting, sedation, pruritis and urinary retention. Evidence from puplished data. Br J Anaesth 2005; 95:584-91.
3. Rose MA, Kam PC. Gabapentin: pharmacology and its use in pain management. Anaesthesia 2002; 57:451-62.
4. Arikkath J, Campbell KP. Auxillary subunits: essential components of the voltage-gated calcium channel complex. Curr Opin Neurobiol 2003; 13:298-307.
5. Gee NS, Brown JP, Dissanayake VU, et al. The novel anticonvulsant drug, gabapentin (Neurontin), binds to the alpha2delta subunit of a calcium channel. J Biol Chem 1996; 271:5768-76.
6. Taylor CP. The biology and pharmacology of calcium channel alpha-2-delta proteins. CNS Drug Rev 2004; 10:183-8.
7. McClelland D, Evans RM, Barkworth L, Martin DJ, Scott RH. A study comparing the actions of gabapentin and pregabalin on the electrophysiological properties of cultered DRG neurons from neonatal rats. BMC Pharmacol 2004; 4:14.

8. Frampton JE, Scott LJ. Pregabalin: in the treatment of painful diabetic peripheral neuropathy. Drugs 2004; 64:2813-20.
9. Frampton JE, Foster RH. Pregabalin: in the treatment of postherpetic neuralgia. Drugs 2005; 65:111-8.
10. 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.
11. Partridge BJ, Chaplan SR, Sakamoto E, Yaksh TL. Characterization of the effects of gabapentin and 3-isobutyl-g-aminobutyric acid on substance P-induced thermal hyperalgesia. Anesthesiology 1998; 88:196-205.
12. Jun JH, Yaksh TL. The effect of intrathecal gabapentin and 3-isobutyl g-aminobutyric acid on the hyperalgesia obseved after thermal injury in the rat. Anesth Analg 1998; 86:348-54.
13. Field MJ, Holloman EF, McCleary S, Hughes J, Singh L. Evaluation of gabapentin and S-(+)-3-isobutylgaba in a rat model of postoperative pain. J Pharmacol ExpTher 1997; 282:1242-6.
14. Vera-Llonch M, Dukes E, Argoff C, Oster G. Analgesic outcomes in patients with painful diabetic neuropathy or post-herpetic neuralgia receiving pregabalin versus gabapentin. J Pain 2005; 6(3 suppl):S33.
15. Gilron I. Gabapentin and pregabalin for chronic neuropathic and early postsurgical pain: current evidence and future directions. Curr Opin Anesthesiol 2007; 20:456-72.
16. Gajraj NM. Pregabalin: its pharmacology and use in pain management. Anesth Analg 2007; 105:1805-15.
17. Pande AC, Pollack MH, Crockatt J, et al. Placebo-controlled study of gabapentin treatment of panic disorder. J Clin Psychopharmacol 2000; 20:467-71.
18. Pande AC, Davidson JR, Jefferson JW, et al. Treatment of social phobia with gabapentin: a placebo-controlled study. J Clin Psychopharmacol 1999; 19:341-8.
19. Ménigaux C, Adam F, Guignard B, Sessler DI, Chauvin M. Preoperative gabapentin decreases anxiety and improves early functional recovery from knee surgery. Anesth Analg 2005; 100:1394-9.
20. Pandey CK, Sahay S, Gupta D, et al. Preemptive gabapentin decreases postoperative pain after lumbar discoidectomy. Can J Anaesth 2004; 51:986-9.
21. Turan A, Karamanlioğlu B, Memiş D, et al. Analgesic effects of gabapentin after spinal surgery. Anesthesiology 2004; 100:935-8.
22. Pandey CK, Navkar DV, Giri PJ, et al. Evaluation of the optimal preemptive dose of gabapentin for postoperative pain relief after lumbar diskectomy: a randomized, double-blinded, placebo-controlled study. J Neurosurg Anesthsiol 2005; 17:65-8.
23. Turan A, Karamanlioğlu B, Memiş D, et al. The analgesic effects of gabapentin after total abdominal hysterectomy. Anesth Analg 2004; 98:1370-3.
24. Fassoulaki A, Patris K, Sarantapoulos C, Hogan Q. The analgesic effect of gabapentin and mexiletine after breast surgery for cancer. Anesth Analg 2002; 95:985-91.
25. Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. A randomized controlled trial of perioperative administration of pregabalin for pain after laparoscopic hysterectomy. Pain 2008; 134:106-12.
26. Reuben SS, Buvanendran A, Kroin JS, Raghunathan K. The analgesic efficacy of celecoxib, pregabalin, and their combination for spinal fusion surgery. Anesth Analg 2006; 103:1271-7.
27. Hill CM, Balkenohl M, Thomas DW, et al. Pregabalin in patients with postoperative dental pain. Eur J Pain 2001; 5:119-24.
28. Tiippana EM, Hamunen K, Kontinen VK, Kalso E. Do surgical patients benefit from perioperative gabapentin/pregabalin? A systematic review of efficacy and safety. Anesth Analg 2007; 104:1545-56.
29. Peng PW, Li C, Farcas E, et al. Use of low-dose pregabalin in patients undergoing laparoscopic cholecystectomy. Br J Anaesth 2010; 105:155-61.
30. Turan A, Memiş D, Karamanlioğlu B, et al. The analgesic effects of gabapentin in monitored anesthesia care for ear-nose-throat surgery. Anesth Analg 2004; 99:375-8.
31. Burke SM, Shorten GD. Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg 2010; 110:1180-5.
32. Pandey CK, Priye S, Singh S, et al. Preemptive use of gabapentin significantly decreases postoperative pain and rescue analgesic requirements in laparoscopic cholecystectomy. Can J Anaesth 2004; 51:358-63.
33. Mathiesen O, Jacobsen LS, Holm HE, et al. Pregabalin and dexamethasone for postoperative pain control: a randomized controlled study in hip arthroplasty. Br J Anaesth 2008; 101:535-41.
34. Alfonsi P. Postanaesthetic shivering: epidemiology, pathophysiology and approaches to prevention and management. Drugs 2001; 61:2193-205.
35. Alfonsi P, Sessler DI, Manoir BD, et al. The effects of meperidine and sufentanil on the shivering threshold in postoperative patients. Anesthesiology 1998; 89:43-8.
36. Wrench IJ, Cavill G, Ward JE, Crossley AW. Comparison between alfentanil, pethidine and placebo in the treatment of post-anaesthetic shivering. Br J Anaesth 1997; 79:541-2.
37. Dal D, Kose A, Honca M, et al. Efficacy of prophylactic ketamine in preventing postoperative shivering. Br J Anaesth 2005; 95:189-92.
38. Kranke P, Eberhart LH, Roewer N, Tramèr MR. Pharmacological treatment of postoperative shivering: A quantitative systematic review of randomized controlled trials. Anesth Analg 2002; 94:453-60.
39. Sessler DI. Temperature monitoring. In: Miller RD, ed. Anesthesia. New York: Churchill Livingstone, 1994: 1363-82.