Journal of Clinical Anesthesia (2016) **31**, 149–153

Journal of Clinical Anesthesia

Original contribution

A randomized placebo-controlled study of preoperative pregabalin for postoperative analgesia in patients with spinal surgery☆

Nao Fujita MD (Stuff Anesthesiologist)[a,1], Masaru Tobe MD (Assistant Professor)[b,1], Noboru Tsukamoto MD (Stuff Anesthesiologist)[a], Shigeru Saito MD (Professor)[b], Hideaki Obata MD (Associate Professor)[b,*]

[a]*Department of Anesthesiology, Keiyu Orthopedic Hospital, 1741 Hanetsuku-cho, Tatebayashi, Gunma 374-0001, Japan*
[b]*Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan*

Received 8 April 2015; revised 22 June 2015; accepted 12 January 2016

Keywords:
Lumbar spinal surgery;
Postoperative pain;
Pregabalin

Abstract
Study objective: To determine whether single preoperative administration of 2 different doses of pregabalin (75 and 150 mg) could decrease postoperative pain intensity and opioid consumption following posterior lumbar interbody fusion surgery.
Design: Prospective, randomized, active placebo-controlled, double-blinded study.
Setting: Postoperative recovery area and patients' room.
Patients: Ninety-seven adult, American Society of Anesthesiologists physical status 1 and 2 patients.
Interventions: Patients were randomly assigned to receive diazepam 5 mg as an active placebo (D5), pregabalin 75 mg (P75), or pregabalin 150 mg (P150). The study drug was orally administered 2 hours prior to surgery and a standard anesthetic technique was used. Postoperative pain was managed using intravenous patient-controlled analgesia with morphine.
Measurement: The visual analog scale at rest was used to measure pain intensity immediately after extubation at the postanesthesia care unit, and then 2, 4, 6, 12, 18, 24, 36, and 48 hours after surgery. Morphine consumption and adverse effects were assessed until 48 hours after surgery.
Main results: The visual analog scale score at rest was lower in the P150 group than in the D5 group until 2 hours after surgery. Morphine consumption was lower in the P150 group than in the D5 from 0 to 12 hours after surgery.
Conclusions: Single preoperative administration of 150 mg of pregabalin 2 hours prior to surgery reduced postoperative pain intensity and morphine consumption compared with 5 mg diazepam in patients who underwent posterior lumbar interbody fusion.

1. Introduction

Despite recent advances in the pharmacology of analgesics and pain control techniques, postoperative pain is still an unmet medical need. A recent study showed that 54% of patients had

☆ Disclosures: The authors have no conflict of interest. This work was supported by individual funding.
* Corresponding author at: Department of Anesthesiology, Gunma University Graduate School of Medicine, 3-39-22, Showa-machi, Maebashi, Gunma 371-8511, Japan. Tel.: +81 27 220 8454; fax: +81 27 220 8473.
E-mail address: hobata@gunma-u.ac.jp (H. Obata).

http://dx.doi.org/10.1016/j.jclinane.2016.01.010
0952-8180/

moderate to extreme pain after surgery at hospital discharge [1]. Opioids are the mainstay of treating postoperative pain, but their use is limited because of adverse effects such as nausea, vomiting, sedation, and pruritis. Multimodal and preemptive analgesia strategies using nerve block and intravenous or oral analgesics have been suggested to reduce opioid-related adverse effects. One of these multimodal analgesia techniques involves the administration of gabapentinoids such as gabapentin and pregabalin [2,3], which were originally introduced as anticonvulsants drugs and bind to the α_2-delta subunit of presynaptic voltage-gated calcium channels [4]; both of these drugs are indicated for the treatment of neuropathic pain [5].

Recently, gabapentin has been used in many prospective randomized trials that evaluated its effectiveness for postoperative pain [6–8]. Perioperative administration of a lower dose of pregabalin than that of gabapentin may provide similar analgesic effects for postoperative pain [9]. However, the analgesic effect of pregabalin for postoperative pain has not been well examined. In this study, we evaluated the dose-related effect of a preoperative single oral administration of pregabalin on postoperative pain intensity and morphine consumption in patients undergoing elective posterior lumbar interbody fusion (PLIF) surgery.

2. Materials and methods

A prospective, randomized, double-blinded, active-controlled trial was conducted at Keiyu Orthopedic Hospital. The study was approved by the Keiyu Orthopedic Hospital Research Ethics Board and registered to the UMIN Clinical Trials Registry (UMIN000010506). After written informed consent was obtained, patients scheduled to undergo PLIF were enrolled in this study. The study population included patients aged 20 to 79 years who were American Society of Anesthesiologists physical statuses I-II and who agreed to participate in this clinical trial. Patients who failed to cooperate, regularly used certain drugs (pregabalin, gabapentin, tricyclic antidepressants, and opioids), and had a history of allergy to any of the study medications, renal dysfunction (serum creatinine >1.2 mg/dL), or body mass index >40 kg/m^2 were excluded.

Preoperative visits were conducted for all of the patients by an anesthesiologist, and the patients were instructed in the use of a visual analog scale (VAS) for pain assessment (0, no pain; 100, worst pain imaginable) and a system for patient-controlled analgesia. The patients were randomly divided into 1 of 3 groups according to treatment: diazepam 5 mg (D5) as an active placebo, pregabalin 75 mg (P75), or pregabalin 150 mg (P150). An anesthesiologist who was not engaged in perioperative patient management or data analysis performed the randomization by drawing lots.

On the day of surgery, intravenous access was established using a 20-G intravenous cannula in the patient's room. Pregabalin (75 or 150 mg) or diazepam (5 mg) was given orally with 10 mL of water 2 hours before surgery. When the patient entered the surgery room, the electrocardiogram, blood pressure, and peripheral oxygen saturation were monitored. Induction of anesthesia was performed with propofol 1.5 to 2.0 mg/kg and infusion of remifentanil 0.25 to 0.4 μg kg^{-1} min^{-1}. Endotracheal intubation was established with rocuronium 0.5 to 0.6 mg/kg, and patients were mechanically ventilated with a mixture of oxygen and air. Sevoflurane was used for maintenance of anesthesia, and remifentanil was infused continuously at 0.1 to 0.3 μg kg^{-1} min^{-1} depending on the vital signs. Each patient received 0.1 mg of fentanyl and 50 mg of flurbiprofen intravenously 10 minutes prior to wound closure.

When the surgery was completed, the remifentanil infusion and sevoflurane inhalation were discontinued and the patient was ventilated with 100% O_2 at a fresh gas flow rate of 6 L/min. The patient was then moved to the postanesthesia care unit and residual neuromuscular block was reversed with sugammadex (2 mg/kg), and then patient was extubated when adequate spontaneous ventilation was established. Patients were connected to the patient-controlled analgesia device (CADD Legacy; Smith Medical Japan, Tokyo, Japan) and administered morphine (1-mg bolus dose, 10-minute lockout time) intravenously, via the device. If pain relief was inadequate, indomethacin suppositories (50 mg, first choice) and pentazocine hydrochloride (15 mg intramuscular, second choice) were administered on patient request as supplementary analgesics. For nausea/vomiting, metoclopramide (10 mg) was intravenously administered on patient request.

After recovery from anesthesia, all patients were observed by nursing staff unaware of the group assignment. The VAS at rest was recorded immediately after extubation at the postanesthesia care unit, and then 2, 4, 6, 12, 18, 24, 36, and 48 hours after surgery in the patient's room. Adverse effects such as nausea and vomiting, sedation, dizziness, headache, or visionary disorder were documented on occurrence. The times of supplementary analgesic usage over a 48-hour period were recorded.

2.1. Statistical analysis

The primary outcome was pain at rest and the secondary outcome was morphine consumption after surgery. The sample size calculation was based on a previous study [10]. Assuming α = .05 and 80% power, an a priori sample size calculation indicated that 28 patients in each group were required. All continuous data within the groups were normally distributed, and the within-group variance was equal across groups. The normality of the data distribution was analyzed by the Shapiro-Wilk test. Continuous data were analyzed using 1-way or 2-way analyses of variance (ANOVAs), followed by Student t test with Bonferroni correction for group comparisons. Categorical data were analyzed using Pearson χ^2 test. Statistical significance was defined as $P < .05$.

3. Results

In total, 97 patients who received posterior PLIF were recruited for this study. One level was operated on in 64 patients

(eg, the L3 and L4 interbodies were fused), 2 levels in 29 patients, and 3 levels in 4 patients. Eight patients were withdrawn from the study because they were uncooperative with the VAS assessment. Consequently, 89 patients completed the study and were included in the final analysis. Fig. 1 illustrates the flow of the patients through the trial, including the reasons for exclusion. The data on the patient characteristics did not differ among the 3 study groups (Table).

The VAS score at rest was lower in the P150 group than in the other groups from 0 to 48 hours after surgery ($P < .001$ by 2-way ANOVA). In the time-point comparisons, the VAS score at rest was lower in the P150 group than in the other groups ($P < .05$ by Student t test with Bonferroni correction) at 0 hours (immediately after extubation), and than in the control (D5) group ($P < .001$ by Student t test with Bonferroni correction) 2 hours after surgery (Fig. 2). Morphine consumption was lower in the P150 group than in the control group from 0 to 12 hours after surgery ($P = .0022$ by Student t test with Bonferroni correction after 1-way ANOVA). Although there was no difference in morphine consumption from 12 to 48 hours after surgery among the 3 groups, the total morphine consumption during 48 hours after surgery was lower in the P150 group than in the control group ($P = .0091$ by Student t test with Bonferroni correction after 1-way ANOVA; Fig. 3). The number of patients who received supplementary analgesics up to 48 hours after surgery in the D5, P75, and P150 groups was 13 (44.8 %), 18 (60 %), and 17 (56.6 %), respectively.

The number of patients who received metoclopramide for nausea/vomiting up to 48 hours after surgery in the D5, P75, and P150 groups was 1, 2, and 2, respectively. One patient in the P150 group complained of dizziness on the day of surgery. None of the patients complained of other adverse effects such as sedation, headache, or vision disorders in this study.

4. Discussion

The main findings in this study were that patients who received a single dose of pregabalin (150 mg) 2 hours before PLIF surgery had lower pain scores than did the control group receiving the active placebo (diazepam 5 mg) and patients receiving a lower dose of pregabalin (75 mg). We also found that these patients required less intravenous patient-controlled morphine analgesia during the 48 hours after surgery.

Meta-analyses have indicated that gabapentinoids consistently show beneficial effects in reducing postoperative pain [6–9], including that after spinal surgery [11]. Several studies have demonstrated that a preoperative single administration of pregabalin reduces the intensity of postoperative pain. For example, administration of 300 mg of pregabalin was shown to reduce pain intensity after laparoscopic gastric bypass [12], abdominal hysterectomy [13], septoplasty [14], and dacryocyctorhinostomy [15], and also to reduce the area of hyperalgesia after transperitoneal nephrectomy [16] compared with a control group. Positive effects were also observed with 150 mg of pregabalin in patients who underwent lumbar laminectomy [17], lumbar discectomy [18], and laparoscopic sleeve gastrectomy [19] compared with a placebo control. Several studies have examined dose-related effects of preoperative administration of pregabalin. A single administration of 150 mg, but not 75 mg, of pregabalin produced analgesic effects after gynecologic laparoscopic surgery [10]. Another study showed a dose-related analgesic effect of 150 and 300 mg of pregabalin after laparoscopic cholesystectomy [20]. Consistent with these studies, we demonstrated that a single preoperative administration of 150 mg of pregabalin reduced VAS scores at rest compared with 5 mg of diazepam up to 2 hours after surgery. These data suggest that a dose of at least 150 mg is necessary to

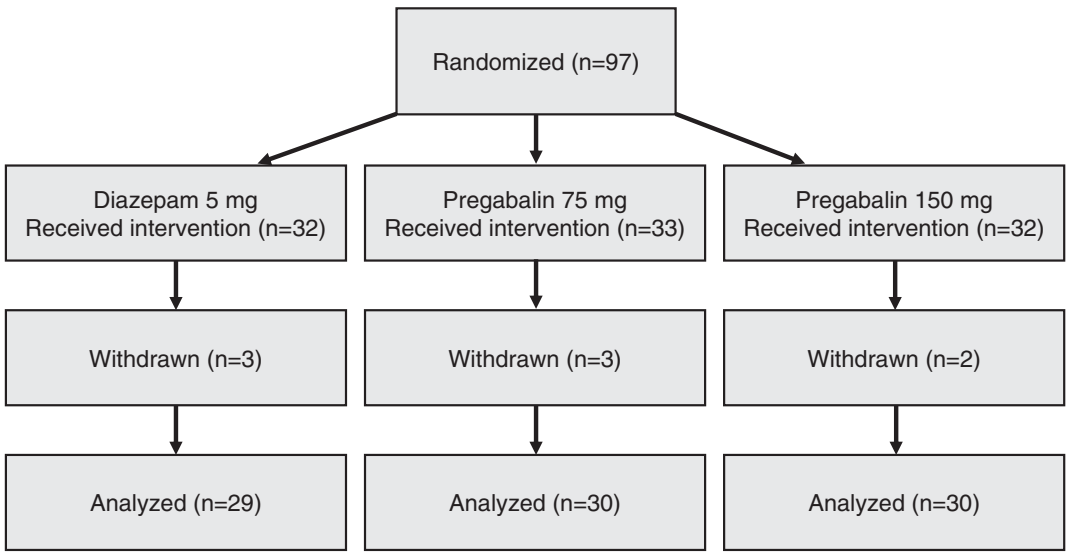

Fig. 1 Patient flow.

Table Patient characteristics.

	D5 (n = 29)	P75 (n = 30)	P150 (n = 30)	*P*
Age (y)	65.4 ± 2.4	59.9 ± 13.7	60.9 ± 9.5	.337
Sex (male/female)	10:19	10:20	12:18	.848
ASA class (I/II)	15/14	12/18	16/14	.363
Height (cm)	157.3 ± 7.2	158.4 ± 7.2	158.5 ± 10.1	.820
Weight (kg)	58.4 ± 9.9	59.2 ± 9.9	57.9 ± 10.6	.888
BMI (kg/m^2)	23.7 ± 4.0	23.5 ± 3.2	22.9 ± 2.8	.683
Duration of surgery (min)	126.5 ± 42.7	125.4 ± 40.9	111.8 ± 38.3	.304
Duration of anesthesia (min)	182.9 ± 47.5	175.5 ± 48.3	164.8 ± 40.5	.313
Remifentanyl (mg)	1.4 ± 0.65	1.3 ± 0.46	1.2 ± 0.65	.292

Data are expressed by mean ± SD or numbers. No significant differences were found between groups.
BMI = body mass index; ASA = American Society of Anesthesiologists; D5 = diazepam 5 mg–treated group; P75 = pregabalin 75 mg–treated group; P150, pregabalin 150 mg–treated group.

reduce postoperative pain intensity after a single preoperative administration of pregabalin.

A meta-analysis previously showed that perioperative multiple administration of pregabalin reduces postoperative morphine consumption [9]. Various other studies have also shown that preoperative single administration of pregabalin at doses of 300 mg [13–16] and 150 mg [17–20] reduces postoperative opioid consumption. The present study clearly demonstrated that preoperative single administration of 150 mg of pregabalin reduced postoperative morphine consumption until 12 hours after surgery. Although there was no difference among the 3 groups in the period from 12 to 48 hours after surgery, the total morphine consumption until 48 hours after surgery was lower in the P150 group than in the group receiving 5 mg of diazepam. These results suggest that a single preoperative administration of pregabalin not only reduces pain intensity but also has an opioid sparing effect during the postoperative period.

The mechanisms by which a single administration of pregabalin reduces postoperative pain are not clear. The gabapentinoids bind to the α_2-δ subunit of presynaptic voltage-gated calcium channels, which are up-regulated in the dorsal horn of the spinal cord after nerve injury in animals [21]. However, this mechanism is not suitable to explain the acute analgesic effect of pregabalin in postoperative pain because the up-regulation of the α2-δ subunit after injury requires several days. Several lines of evidence have indicated that the antinociceptive effect of gabapentinoids may be derived from activation of the noradrenergic descending inhibitory pathway [22,23], and that gabapentin suppresses postoperative pain in animal models via a spinal noradrenergic mechanism [24]. Although there is no evidence to indicate that pregabalin produces an acute antinociceptive effect, this mechanism could explain the analgesic effect of pregabalin in postoperative pain.

In the present study, it remains unclear whether the effect of preoperative administration of pregabalin was exerted through preemptive analgesia, which is based on the concept that "antinociceptive treatment given before incision is more effective than that given after" or "perioperative antinociceptive

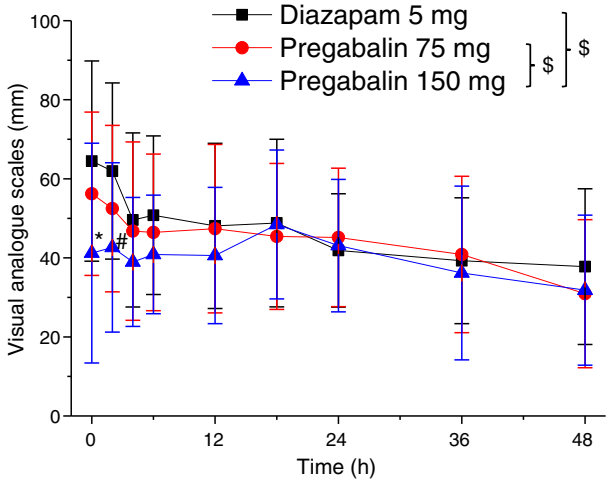

Fig. 2 Mean (±SD) visual analogue scale score at rest during the first 48 hours after surgery. *$P < .05$ vs the other 2 groups; $^{\#}P < .05$ vs diazepam 5 mg group; $^{\$}P < .01$ between 2 groups by Student *t* test with Bonferroni correction.

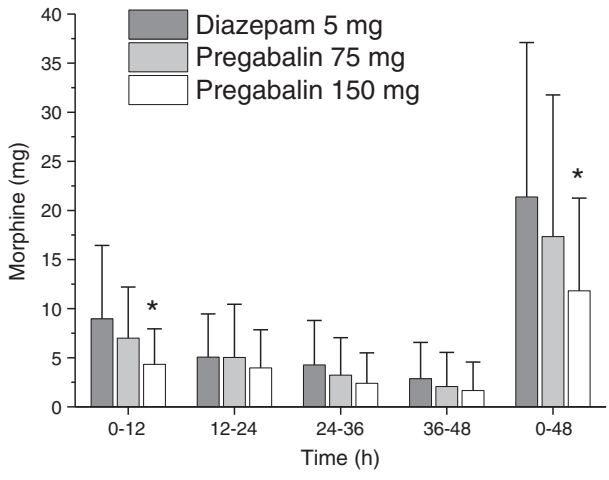

Fig. 3 Mean (±SD) cumulative morphine consumption at each time point after surgery. *$P < .05$ by Student *t* test with Bonferroni correction after 1-way analysis of variance compared with diazepam 5 mg group.

treatment reduces subsequent postoperative pain" [25]. Future studies should thus examine whether pregabalin has the ability to produce a preemptive effect against acute postoperative pain in addition to a reduction of the incidence of chronic postsurgical pain.

There are several limitations in this study. First, we only determined VAS scores for resting pain to evaluate postoperative pain intensity. Dynamic pain and other pain-related parameters such as hyperalgesia and mechanical pain threshold were not examined. Second, although there was no difference among the 3 groups, the evaluation of potential adverse effects was insufficient. Third, the body size (height and weight) of patients included in this study was relatively smaller than that in previous studies, which makes it difficult to determine a standard dose for preoperative pregabalin. However, our primary intent was to determine whether preoperative pregabalin has an analgesic effect against postoperative pain. Although the methodology of the present study was simple, we clearly showed a positive effect of a preoperative single administration of pregabalin for postoperative pain.

In summary, we demonstrated that a single preoperative administration of 150 mg of pregabalin 2 hours prior to surgery produced analgesic effects in patients who underwent PLIF. Further studies on pregabalin in this field should focus on preemptive effects against acute postoperative pain, the incidence of opioid-related adverse effects, and preventive effects against chronic postsurgical pain.

Acknowledgments

We thank Dr Devang Thakor of Anioplex, LLC, for English editing.

References

[1] Buvanendran A, Fiala J, Patel KA, Golden AD, Moric M, Kroin JS. The incidence and severity of postoperative pain following inpatient surgery. Pain Med 2015;12:2277-83.
[2] Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol 2009;22:588-93.
[3] Penprase B, Brunetto E, Dahmani E, Forthoffer JJ, Kapoor S. The efficacy of preemptive analgesia for postoperative pain control: a systematic review of the literature. AORN J 2015;101:94-105.
[4] Taylor CP. Mechanisms of analgesia by gabapentin and pregabalin—calcium channel alpha2-delta [Cavalpha2-delta] ligands. Pain 2009;142:13-6.
[5] Dworkin RH, O'Connor AB, Backonja M, Farrar JT, Finnerup NB, Jensen TS, et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132:237-51.
[6] Ho KY, Gan TJ, Habib AS. Gabapentin and postoperative pain—a systematic review of randomized controlled trials. Pain 2006;126:91-101.
[7] Mathiesen O, Møiniche S, Dahl JB. Gabapentin and postoperative pain: a qualitative and quantitative systematic review, with focus on procedure. BMC Anesthesiol 2007;7:6.
[8] 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.
[9] Zhang J, Ho KY, Wang Y. Efficacy of pregabalin in acute postoperative pain: a meta-analysis. Br J Anaesth 2011;106:454-62.
[10] Jokela R, Ahonen J, Tallgren M, Haanpää M, Korttila K. Premedication with pregabalin 75 or 150 mg with ibuprofen to control pain after day-case gynaecological laparoscopic surgery. Br J Anaesth 2008;100:834-40.
[11] Yu L, Ran B, Li M, Shi Z. Gabapentin and pregabalin in the management of postoperative pain after lumbar spinal surgery: a systematic review and meta-analysis. Spine (Phila Pa 1976) 2013;38:1947-52.
[12] Alimian M, Imani F, Faiz SH, Pournajafian A, Navadegi SF, Safari S. Effect of oral pregabalin premedication on post-operative pain in laparoscopic gastric bypass surgery. Reg Anesth Pain Med 2012;2:12-6.
[13] Ittichaikulthol W, Virankabutra T, Kunopart M, Khamhom W, Putarawuthichai P, Rungphet S. Effects of pregabalin on post operative morphine consumption and pain after abdominal hysterectomy with/without salphingo-oophorectomy: a randomized, double-blind trial. J Med Assoc Thai 2009;92:1318-23.
[14] Demirhan A, Akkaya A, Tekelioglu UY, Apuhan T, Bilgi M, Yurttas V, et al. Effect of pregabalin and dexamethasone on postoperative analgesia after septoplasty. Pain Res Treat 2014;2014:850794.
[15] Alimian M, Imani F, Hassani V, Rahimzadeh P, Sharifian M, Safari S. Effects of single-dose pregabalin on postoperative pain in dacryocystorhinostomy surgery. Reg Anesth Pain Med 2012;2:72-6.
[16] Bornemann-Cimenti H, Lederer AJ, Wejbora M, Michaeli K, Kern-Pirsch C, Archan S, et al. Preoperative pregabalin administration significantly reduces postoperative opioid consumption and mechanical hyperalgesia after transperitoneal nephrectomy. Br J Anaesth 2012;108:845-9.
[17] Kumar KP, Kulkarni DK, Gurajala I, Gopinath R. Pregabalin versus tramadol for postoperative pain management in patients undergoing lumbar laminectomy: a randomized, double-blinded, placebo-controlled study. J Pain Res 2013;6:471-8.
[18] Spreng UJ, Dahl V, Raeder J. Effect of a single dose of pregabalin on post-operative pain and pre-operative anxiety in patients undergoing discectomy. Acta Anaesthesiol Scand 2011;55:571-6.
[19] Cabrera Schulmeyer MC, de la Maza J, Ovalle C, Farias C, Vives I. Analgesic effects of a single preoperative dose of pregabalin after laparoscopic sleeve gastrectomy. Obes Surg 2010;20:1678-81.
[20] Balaban F, Yağar S, Özgök A, Koç M, Güllapoğlu H. A randomized, placebo-controlled study of pregabalin for postoperative pain intensity after laparoscopic cholecystectomy. J Clin Anesth 2012;24:175-8.
[21] Luo ZD, Calcutt NA, Higuera ES, Valder CR, Song YH, Svensson CI, et al. Injury type-specific calcium channel alpha 2 delta-1 subunit up-regulation in rat neuropathic pain models correlates with antiallodynic effects of gabapentin. J Pharmacol Exp Ther 2002;303:1199-205.
[22] Tanabe M, Takasu K, Takeuchi Y, Ono H. Pain relief by gabapentin and pregabalin via supraspinal mechanisms after peripheral nerve injury. J Neurosci Res 2008;86:3258-64.
[23] Hayashida K, Obata H, Nakajima K, Eisenach JC. Gabapentin acts within the locus coeruleus to alleviate neuropathic pain. Anesthesiology 2008;109:1077-84.
[24] Hayashida K, DeGoes S, Curry R, Eisenach JC. Gabapentin activates spinal noradrenergic activity in rats and humans and reduces hypersensitivity after surgery. Anesthesiology 2007;106:557-62.
[25] Kissin I. Preemptive analgesia. Why its effect is not always obvious. Anesthesiology 1996;84:1015-9.