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Original Contribution

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

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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

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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 $\mu g\ kg^{-1}\ min^{-1}$. 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 $\mu g\ kg^{-1}\ min^{-1}$ 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 $\alpha = .05$ 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