Early Postoperative Analgesic Effects of a Single Epidural Injection of Ropivacaine Administered Preoperatively in Posterior Lumbar Interbody Spinal Arthrodesis

A Pilot Randomized Controlled Trial

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Background: Despite the suitable characteristics of ropivacaine as an epidural analgesic agent, such as better preservation of motor function and less neurotoxicity, we are aware of no data on its clinical application in pain management following lumbar spine surgery. The purpose of the present study was to evaluate the preemptive analgesic effects and safety of a single epidural injection of ropivacaine during lumbar arthrodesis.

Methods: We performed a randomized, double-blinded, intention-to-treat study. Patients with planned one-level posterior lumbar interbody arthrodesis were randomly assigned to either the injection group (n = 32) or the control group (n = 34). The injection group received a 10-mL epidural injection of 0.1% ropivacaine twenty minutes before the skin incision at the planned vertebral level, and the control group received an epidural injection of 10 mL of 0.9% saline solution. A numeric rating scale (from 0 to 10) was measured at seven time points after surgery (at two, four, eight, twelve, twenty-four, and forty-eight hours and at the time of discharge), and the frequency of pushed-button patient-controlled analgesia and total fentanyl consumption were assessed at similar time points (up to two, up to four, up to eight, up to twelve, up to twenty-four, and up to forty-eight hours after surgery). Postoperative nausea and vomiting, the duration of the hospital stay, and the Likert satisfaction score at the time of discharge were evaluated.

Results: There were no significant differences between the two groups preoperatively. The numeric rating scale score was higher until twelve hours (p < 0.05) and the frequency of button pushes was higher at every time point except eight to twelve hours (p < 0.05) in the control group as compared with the injection group. Fentanyl consumption until eight to twelve hours (p < 0.05) and total consumption (p < 0.001) at discharge were higher in the control group. There were no differences between the two groups in terms of postoperative nausea and vomiting, the duration of hospital stay, or the mean satisfaction score, and no transient motor weakness was seen in relation to epidural injection of ropivacaine.

Conclusions: A single-dose epidural injection of 0.1% ropivacaine before lumbar spine surgery is effective for reducing early postoperative pain without related complications such as transient motor weakness.

Level of Evidence: Therapeutic Level I. See Instructions for Authors for a complete description of levels of evidence.

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A commentary by Michael J. Bolesta, MD, is linked to the online version of this article at jbjs.org.
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ostoperative pain management following spinal surgery has been a main concern because it is closely related to surgical outcome and could be the cause of persistent chronic postoperative pain\(^1\)–\(^4\). To effectively control early postoperative pain, parenteral opioids have been a mainstay, although various multimodal pain management protocols have been developed\(^5\)–\(^7\). However, these opioids have been associated with potential complications, such as nausea and cognitive impairment, as well as potentially severe complications, including respiratory depression, hypotension, and urinary retention\(^8\)–\(^10\).

To reduce opioid-related complications, one element in multimodal pain treatment has been the use of local anesthetics, especially in the form of preemptive analgesia\(^1\)–\(^4\),\(^7\)–\(^9\). Their application, either to block the neural transmission of pain signals or to desensitize local nociceptors, is an efficient way of reducing postoperative pain perception\(^1\)–\(^6\),\(^11\)–\(^14\). Considering that the goal of preemptive analgesia is preventing central sensitization, the use of local anesthetics in the form of epidural injection could be effective for blocking the central responses. However, the main limitations of epidural analgesia with use of local anesthetics are the possibility of postoperative transient motor block and indwelling catheter problems\(^5\),\(^12\)–\(^14\).

Ropivacaine, a long-acting amide local anesthetic, may be very suitable for epidural anesthesia to reduce postoperative pain following spinal surgery because it better preserves motor function when used in nerve blocks and is associated with less cardiovascular and central nervous system toxicity\(^5\),\(^10\)–\(^12\).

Despite the suitable characteristics of ropivacaine as an epidural analgesic agent in postoperative pain management, we are aware of no clinical trial that has evaluated the efficacy of epidural ropivacaine injection as preemptive analgesia in lumbar spine surgery. The purpose of the present study was to investigate the preemptive analgesic effects of a single epidural ropivacaine injection on the intensity of postoperative pain and the reduction of parenteral opioid requirements in the early postoperative period following one-level posterior lumbar interbody arthrodesis.

### Materials and Methods

The study protocol was approved by the ethics committee at our hospital and was registered in the ClinicalTrials.gov Protocol Registration System (NCT01117610). Written informed consent was obtained from all of the participants before inclusion in the trial. The research was conducted between June 2010 and July 2011.

The inclusion criterion was a planned one-level posterior lumbar interbody arthrodesis with decompression for the treatment of severe stenosis and/or spondylolisthesis accompanied by segmental instability, with the patient under general anesthesia. The decision for surgery was made by one author (K.-S.S.). Patients who weighed <45 or >100 kg; who had severe underlying respiratory, renal, or hepatic disease; or who had a history of allergy to local anesthetics were excluded from the study. Additional exclusion criteria included a history of opioid medication in the previous month or a psychiatric medical history.

The patients were randomly assigned to either the injection group (n = 30) or the control group (n = 30) according to the drawing of sequentially numbered, opaque, sealed envelopes, each of which contained a code based on a computer-generated random-number list.

After admission to the operating room and just before the induction of anesthesia, the appropriate numbered envelope was opened, and the card inside determined whether the patient would be in the control group or the injection group. Ropivacaine or normal saline solution was then prepared by the nurse in the form of syringes labeled with the case number.

Postoperative data acquisition during follow-up was performed by another investigator (J.J.Y.), who was blinded to the details of the randomization. All patients received the same anesthetic protocol. The patients did not receive premedication, and anesthesia was induced with fentanyl (2 \(\mu g/kg\)), thiopental (5 mg/kg), and rocuronium (0.6 mg/kg). The trachea was intubated, and ventilation was controlled at a tidal volume of 10 mL/kg and at a respiratory rate of 10 breaths/minute. Anesthesia was maintained with use of 2% to 3% sevoflurane and 50% nitrous oxide in oxygen. During the surgery, patients

### TABLE I Postoperative Variables

<table>
<thead>
<tr>
<th></th>
<th>Control Group* (N = 34)</th>
<th>Injection Group* (N = 32)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total frequency of pushed buttons† (no. of pushes)</td>
<td>34.50 (24.50 to 44.25)</td>
<td>17.00 (13.00 to 24.00)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Fentanyl ((\mu g))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total dose</td>
<td>777.62 ± 169.02</td>
<td>601.63 ± 144.19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Patient-controlled analgesia dose</td>
<td>712.92 ± 164.96</td>
<td>570.38 ± 139.14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rescue dose†</td>
<td>50.00 (0.00 to 100.00)</td>
<td>0.00 (0.00 to 50.00)</td>
<td>0.020</td>
</tr>
<tr>
<td>Rescue dose needed (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>22</td>
<td>12</td>
<td>0.027</td>
</tr>
<tr>
<td>No</td>
<td>12</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Motor weakness (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>6</td>
<td>0.312</td>
</tr>
<tr>
<td>No</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Postoperative nausea and vomiting (no. of patients)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>10</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>24</td>
<td>26</td>
<td></td>
</tr>
<tr>
<td>Hospital stay† (d)</td>
<td>9.00 (7.00 to 14.00)</td>
<td>8.50 (6.00 to 12.25)</td>
<td>0.406</td>
</tr>
<tr>
<td>Likert satisfaction score†</td>
<td>2.00 (1.00 to 3.00)</td>
<td>2.00 (2.00 to 2.75)</td>
<td>0.867</td>
</tr>
</tbody>
</table>

* The values are expressed as the mean and the standard deviation, the median and the interquartile range, or the absolute number. † The Mann-Whitney U test was used and the values are expressed as the median and interquartile range because of abnormal distribution.
received intravenous infusion of lactated Ringer solution at a rate of 4 to 8 mL/kg/hour. No additional intravenous opioids were injected.

A 21-gauge hypodermic needle was then introduced into the epidural space by one of the authors (H.K.) with the patient in the prone position on the same operation table with use of the loss of resistance technique. The injection group received an epidural injection of 0.1% ropivacaine (10 mL), twenty minutes before skin incision at the planned operative spine level, and the control group received an epidural injection of 0.9% saline solution (10 mL) in the same manner. Accurate placement into the space was verified with the injection of contrast medium (iohexol, 180 mgI/mL) under fluoroscopic guidance.

The surgical technique was as follows. A midline skin incision followed by subperiosteal dissection was bilaterally performed at the facet joints. Thus, the transverse processes were not fully exposed. Pedicle screws were inserted and bilateral facetectomy was performed for foraminal decompression, followed by disc removal and the placement of two intervertebral cage devices filled with autogenous bone. An autogenous bone graft from the posterior superior iliac spine and local bone obtained at the time of decompression were used to fill the disc space and cages in all patients.

To control postoperative pain, a computerized intravenous patient-controlled analgesia system (Automed 3300; AceMedical, Seoul, South Korea) was used. The mode of the patient-controlled analgesia was a 0.125-μg/kg bolus dose with a lockout interval of fifteen minutes and 0.125 μg/kg/h (total regimen of 100 mL continuous infusion of fentanyl). The patients were preoperatively instructed on the use of the patient-controlled analgesia. The frequency with which the button was pushed was recorded by the patient-controlled analgesia system. In the case of persistent pain with a numeric rating of >4 (on a scale from 0 to 10), even under controlled patient-controlled analgesia, an additional 50 μg of fentanyl (rescue dose) was injected intravenously until the pain was relieved to a level of <4. Although we administered postoperative patient-controlled analgesia and rescue analgesia, some patients reported a rating of >4 in the immediate postoperative period. In these cases, the numeric rating was recorded as it was, and patients were given an additional injection of fentanyl if desired. No other kinds of analgesics were used.

For each patient, we preoperatively recorded age, sex, the American Society of Anesthesiologists (ASA) physical status, the numeric rating for back pain, and the Oswestry Disability Index. The operative time from skin incision to closure was recorded after surgery.

To measure pain intensity after surgery, the numeric rating was recorded by a blinded investigator at seven time points: two, four, eight, twelve, twenty-four, and forty-eight hours after surgery and at the time of discharge. The frequency of pushed buttons and the total amount of fentanyl used (the sum of rescue analgesia and patient-controlled analgesia) were assessed at similar time points (up to two, up to four, up to eight, up to twelve, up to twenty-four, and up to forty-eight hours after surgery). The presence of transient motor and sensory deficits during the immediate postoperative period and the frequency of postoperative nausea and vomiting treated with intravenous delivery of antiemetics (Ondansetron HCl; Hanmi, Seoul, South Korea) (4 mg) were evaluated. In addition, the duration of hospital stay and the Likert

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CONSORT diagram. PONV = postoperative nausea and vomiting. Group C = control group and Group I = injection group.
satisfaction score for postoperative pain control (with 1 corresponding with “completely comfortable,” 2 corresponding with “quite comfortable,” 3 corresponding with “slight discomfort,” 4 corresponding with “painful,” and 5 corresponding with “very painful”) at the time of discharge were measured. C-reactive protein was routinely examined on the day before surgery and at one, three, and five days postoperatively.

Statistical Methods
To estimate group size, a pilot study was conducted to obtain the numeric rating at four hours after surgery for ten patients who did not receive any medication. The standard deviation of the numeric rating in this group was 2.8. For our power calculation, we assumed equal standard deviations in the control group and the injection group. We wanted to be able to show a difference of 2 in the numeric rating scale pain scores at four hours after surgery between groups. With $\alpha = 0.05$ (two tailed) and a power of 80%, we needed thirty patients per group; hence, a total of sixty patients were included in this study.

We used an intention-to-treat strategy—that is, all participants were included in the analysis irrespective of whether they had completed the study. Missing data were completed with use of a last observation carried forward analysis. Associations between the numeric rating scale, the frequency of pushed buttons, and fentanyl consumption were analyzed with use of as-treated strategy.

For intergroup comparisons, the distribution of the data was first evaluated for normality with use of the Shapiro-Wilk test. Normally distributed data are presented here as the mean and the standard deviation, and groups were compared with use of the Student t test. Non-normally distributed data are expressed as the median and the interquartile range and were analyzed with use of the Mann-Whitney U test. Descriptive variables were subjected to chi-square analysis or the Fisher exact test, as appropriate. Associations between the numeric rating scale, the frequency of pushed buttons, and fentanyl consumption at each time interval were evaluated with use of the Spearman rank correlation coefficient ($\rho$). The level of significance was set at $p < 0.05$. Data in the figures are reported as the mean and the standard error. Statistical analysis was performed with use of SPSS software (version 18.0; SPSS, Chicago, Illinois).

Source of Funding
No funding was received for the present study.

Results
There were no significant differences between the two groups with respect to age, height, weight, sex, ASA class, operative time, operative level, preoperative numeric rating scale score, or Oswestry Disability Index (see Appendix). Six patients were excluded from the study. Four patients (three in the control group and one in the injection group) were managed with other analgesics because of postoperative nausea and vomiting that was unresponsive to antiemetic treatment and likely was induced by fentanyl injection, and two patients (one in each group) were not cooperative because of immediate postoperative delirium. Subsequently, six patients who met the inclusion criteria replaced the excluded patients (Fig. 1). If an exclusion occurred, the subsequent patient was allocated to the same group as the excluded patient by one of the authors (H.K.), who was aware of the group assignment.

Pain Intensity (Numeric Rating Scale and Frequency of Pushed Buttons)
The highest pain scores were experienced at two hours and gradually diminished over time in both groups. The pain scores were significantly higher in the control group than in the injection group from two to twelve hours ($p < 0.05$) (Fig. 2). The frequency of pushed buttons was higher in the control group than in the injection group at every time point except eight to twelve hours (Fig. 3). In terms of the overall frequency of pushed buttons through forty-eight hours postoperatively, the injection group also showed lower frequency compared with the control group ($p < 0.001$) (Table I). Numeric rating scale scores were positively correlated with the frequency of pushed buttons ($\rho = 0.484$) ($p < 0.001$).
Fentanyl Consumption (Patient-Controlled Analgesia Dose + Rescue Dose)
The amount of fentanyl consumption from patient-controlled analgesia and rescue analgesia decreased gradually in both groups up to forty-eight hours and was higher in the control group than the injection group at every interval up to twelve hours (p < 0.05). With respect to delivery types, the patient-controlled analgesia dose was higher from two to four hours to eight to twelve hours and the rescue dose was higher at zero to two hours and four to eight hours in the control group than the injection group (p < 0.05) (Fig. 4).

In terms of the total amount of injected fentanyl before discharge, the injection group required significantly less analgesia than the control group did (p < 0.001). The total patient-controlled analgesia and rescue doses were both lower in the injection group than in the control group (p < 0.05) (Table I). Numeric rating scale scores were positively correlated with fentanyl consumption ($r = 0.515$, $p < 0.001$).
Postoperative Outcomes

Postoperative nausea and vomiting necessitating treatment with antiemetics was less frequent in the injection group than in the control group, but the differences were not significant. There were also no significant differences with respect to the length of hospital stay and the Likert satisfaction score for postoperative pain control at the time of discharge (Table I). There was no morbidity or perioperative motor weakness directly associated with epidural injection. Postoperative C-reactive protein was significantly higher in the control group than the injection group on the third postoperative day (p = 0.016) (see Appendix).

Discussion

Postoperative pain-management protocols should be procedure-specific and evidence-based to effectively control pain. Among the various efforts to reduce postoperative pain after lumbar spinal surgery, the potential convenience and effectiveness of epidural injection is promising because it is inherently simple and because the prone position and the availability of fluoroscopy are ideal for approaching the epidural space. Epidural injection works to block noxious input and to modulate pain processing at the spinal level, which again emphasizes one of the goals of preemptive analgesia as the prevention of central sensitization. Epidural analgesia can be achieved either by placing an epidural catheter or by administering a single epidural injection. Many studies have suggested that a single-dose epidural block could be an effective modality for postoperative pain management. Although an indwelling catheter in the epidural space has the advantage of enabling continuous drug release over the course of a few days, it also has the potential for catheter-related problems, such as local site inflammation, catheter migration, or accidental removal. Another main possible adverse effect of epidural anesthesia is transient motor block, which can confuse the postoperative neurological examination, especially in patients managed with spinal surgery. To address that problem, ropivacaine may be a good candidate for epidural analgesia. It is favored over bupivacaine and lidocaine because it better preserves motor function and currently has the greatest margin of safety for cardiovascular and central nervous system toxicity among all long-acting local anesthetics.

However, procedure-related complications, including headache, cerebrospinal fluid leakage, or transient paraplegia caused by ropivacaine with unintentional dural puncture, have been described in other reports. In our study, we used 0.1% ropivacaine (10 mL), which is a lower concentration than was used in other studies. In addition, careful epidural block procedures can minimize the complication, such as epidural hematoma, unintentional intrathecal injection, etc. In the present study, there were no procedure-related complications such as transient motor paralysis or sensory block induced by injection.

The patients who were managed with a single-dose epidural injection of ropivacaine before skin incision at the time of one-level posterior lumbar arthrodesis showed significantly better early postoperative analgesia (as demonstrated by the numeric rating scale score within twelve hours and by the frequency of pushed buttons at every time point except eight to twelve hours) and decreased fentanyl consumption within twelve hours as compared with patients managed with saline solution.

The results of the present study imply that a single epidural injection of ropivacaine before skin incision had meaningful analgesic effects mainly in the early postoperative period until twelve hours in comparison with the control group, even though ropivacaine was not continuously contained in the epidural space because of surgical exploration.

The present study is based on a pretreatment versus no-treatment design to evaluate the preemptive analgesic effect of an epidural injection of a single dose of ropivacaine. Another study design could be based on a pretreatment versus posttreatment design. The outcome differences between the two groups could be of greater magnitude in our design than in the latter design. However, the latter design may lead to a situation in which the establishment of nociception during inflammatory stimuli in the early postoperative period is excluded from consideration.

Interestingly, C-reactive protein was significantly lower in the injection group than the control group on the third postoperative day. This finding suggests the possibility that the anti-inflammatory property of ropivacaine affects the inflammatory reaction caused by surgical insults and could influence the intensity of postoperative pain by lowering the inflammatory reaction, although further study needs to be done to exactly demonstrate it. We restricted the drug used for postoperative pain management to fentanyl to exclude any bias that could occur in association with the use of other analgesics. Fentanyl, a lipophilic opioid, is a popular and effective analgesic agent to control postoperative pain. However, in the present study, there were some cases in which pain was not controlled to a numeric rating scale rating of <4 even with a rescue fentanyl dose (50 µg). This finding suggests that fentanyl mainly acts on the modulation and perception step in the process of nociception and may be insufficient for the control of postoperative pain in some cases because it has little effect on the anti-inflammatory process. These findings demonstrate the importance of using multimodal treatments with influences at different pain pathways to effectively control postoperative pain.

In spite of the early positive analgesic effects of injected ropivacaine, there were no differences between the two groups in terms of the hospital stay (difference in mean, −1.34; 95% confidence interval [CI], −6.09 to 3.40) or the Likert satisfaction score (difference in mean, 2.15; 95% CI, −1.71 to 6.02) at the time of discharge. As we determined the sample size by calculating the power on the basis of the numeric rating scale at four hours in our study, the number of patients included may have been too small to reach a level of significance with regard to such variables or pain intensity in relatively late postoperative periods. This is a limitation of our study.

The results of our study provide evidence that a single epidural injection of 0.1% ropivacaine (10 mL) before one-level posterior lumbar interbody arthrodesis is effective and suitable for reducing early postoperative pain and opioid use without procedure-related complications. This appears to be a good component of multimodal pain management in lumbar spine surgery.
Appendix

A table showing demographic data and preoperative variables and a figure demonstrating the C-reactive protein levels for both groups are available with the online version of this article as a data supplement at jbjs.org.

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References