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Randomized active-controlled study of a single preoperative administration of duloxetine to treat postoperative pain and numbness after posterior lumbar interbody fusion surgery

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Abstract

Background: This prospective, randomized, double-blinded, active controlled trial assessed whether a single preoperative administration of 40 mg of duloxetine could decrease postoperative pain and numbness after posterior lumbar interbody fusion surgery (PLIF).

Methods: Patients with an American Society of Anesthesiologists physical status I or II undergoing PLIF were included. At 2 hours before inducing anesthesia, patients were administered 40 mg duloxetine or 4 mg diazepam (control drug). Postoperative pain and other symptoms were evaluated on the basis of a visual analog scale, amount of fentanyl used, fentanyl dose request times, rate of use of adjunctive analgesics (diclofenac sodium or pentazocine), and lower limb numbness score (0–3) during the first 2 postoperative days.

Results: Forty-six patients were randomly assigned to the duloxetine and diazepam groups (n = 23 each); 6 were lost to follow-up, and analysis was performed on data from 22 patients in the duloxetine group and 18 in the diazepam group. No significant differences were detected in the patient background, postoperative visual analog scale score at rest in the lumbar region and lower limbs, fentanyl use, rate of analgesic adjuvant use, or incidence of side effects. The numbness score in the lower limbs, however, was significantly lower in the duloxetine group.

Conclusion: A single preoperative 40-mg dose of duloxetine did not improve postoperative pain after PLIF, but did improve lower limb numbness. Duloxetine may suppress neuropathic pain-like symptoms after PLIF surgery.

Abbreviations: PCA = patient-controlled analgesia, PLIF = posterior lumbar interbody fusion surgery, VAS = visual analog scale.

Keywords: duloxetine, posterior lumbar interbody fusion surgery, postoperative analgesia

1. Introduction

Postoperative pain may delay postoperative weaning and recovery. Severe pain in the early postoperative period increases the probability of transition to chronic pain, which can significantly affect the quality of life.[1] Although opioids are effective against postoperative pain, side effects such as respiratory depression, nausea, vomiting, and itching limit their use. In addition, opioid dependence triggered by perioperative opioid use is a serious problem,[2] and efforts should be made to reduce opioid use through multimodal analgesia using a variety of analgesics. Duloxetine, a serotonin and noradrenaline reuptake inhibitor, increases noradrenaline and serotonin in the spinal cord, with the noradrenaline increase in particular having analgesic effects on neuropathic pain.[3] Recent studies reported that increasing spinal noradrenaline is not only effective against chronic pain, but is also effective for acute pain, such as postoperative pain.[4–6] In these studies, however, duloxetine administered perioperatively caused side effects such as dizziness, which may delay postoperative recovery.[4] In our previous study, a single oral administration of pregabalin preoperatively reduced acute pain and opioid use in patients that underwent lumbar interbody fusion (PLIF) surgery compared with a control group.[7] Because oral duloxetine has a long half-life (10.6 hours), the effects of preoperative administration before surgery may persist after surgery. Whether duloxetine administered preoperatively can improve postoperative pain,

TH and NF contributed equally to this work.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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however, has not yet been evaluated. In the present study, we investigated the effects of a single oral 40-mg dose of duloxetine administered before surgery on the postoperative pain intensity and fentanyl use in patients undergoing PLIF surgery. The primary endpoint was postoperative resting lumbar pain compared with the control group on the basis of a visual analog scale (VAS). The secondary endpoint was the postoperative intravenous patient-controlled analgesia (PCA) fentanyl dose and request time; the administration rate of adjunctive analgesics; lower limb pain and numbness; and postoperative side effects according to the incidence of postoperative dizziness, nausea and vomiting, dry mouth, and confusion, compared with the control group.

2. Methods

This was a prospective, randomized, double-blinded, active controlled trial conducted at Keiyu Orthopedic Hospital. The study protocol was approved by the Fukushima Medical University Research Ethics Board and the Keiyu Orthopedic Hospital Research Ethics Board (RK29008), and registered to the UMIN Clinical Trials Registry (UMIN000031428). Patients with an American Society of Anesthesiologists physical status I or II undergoing PLIF were included. All patients provided written informed consent prior to participating in the study. Study design and reporting conformed to CONSORT (Consolidated Standards of Reporting Trials) standards. Eligible patients were enrolled into the study after reviewing the inclusion and exclusion criteria. Exclusion criteria were as follows: psychiatric disorders such as mania, bipolar disorder, depression, anxiety disorders, eating disorders, or a history of these disorders requiring medication within 1 year prior to enrollment; treatment with antidepressants such as amitriptyline or duloxetine that cannot be stopped for 2 weeks prior to surgery; treatment with opioids that cannot be stopped for 1 week prior to surgery; organic brain disorder, seizure disorder such as epilepsy, or history of these disorders; poorly controlled acute angle glaucoma; inability to understand the study protocol due to psychiatric disorders or dementia; serious cardiovascular (poorly controlled hypertension, history of myocardial infarction or angina, implanted pacemaker, moderate reduction of ejection fraction), hepatic (serum aspartate aminotransferase or alanine aminotransferase > 100 IU/L), renal (serum creatinine > 2 mg/dL), respiratory (history of chronic obstructive pulmonary disease, poorly controlled asthma), or hematologic diseases (hemoglobin concentration < 9.5 g/dL or platelet concentration < 75,000/μL); excessive alcohol intake (average daily consumption > 60 g of alcohol); history of hypersensitivity to duloxetine and diazepam; and treatment with MAO inhibitors and within 2 weeks of completion of treatment. Preoperative visits were made to all patients by an anesthesiologist. During the examination, a VAS was used to assess pain (0: no pain, 100: worst imaginable pain) and numbness (0: no numbness, 1: mild numbness, 2: moderate numbness, 3: strong numbness), and patient-controlled analgesia was explained to the patients. Preoperative lumbar and lower limb pain and lower limb numbness were assessed by the physical therapist using a VAS. Consenting patients were randomly divided into 2 groups and received diazepam (4 mg, control) or duloxetine (40 mg) 2 hours before entering the operating room. The patients were randomized by anesthesiologists who were not involved in the perioperative management or data analysis. Induction of general anesthesia was performed with propofol (1–2 mg/kg), rocuronium (0.9 mg/kg), and remifentanil (0.2–0.3 μg/kg/min), followed by tracheal intubation and positioning in the prone position. General anesthesia was maintained with sevoflurane (1.5%) and remifentanil (0.1–0.3 μg/kg/min). At 20 minutes before wound closure, fentanyl (0.1 mg), flurbiprofen axetil (1 mg/kg; 50 mg for body weight > 50 kg), and acetaminophen (15 mg/kg; 1000 mg for body weight > 50 kg) were administered. After surgery, the patients were shifted to the supine position, and administration of sevoflurane and remifentanil was stopped. The patients were moved to the post-anesthesia care unit and sugammadex (2 mg/kg) was administered to antagonize the effects of the muscle relaxants. Upon confirmation of spontaneous breathing and the ability to follow the instructed movements, the patients were extubated. Patients were connected to the PCA device (CADD Solis PIB; Smith Medical Japan, Tokyo, Japan) and fentanyl (15 μg bolus dose, 10-minute lockout time) was administered intravenously via the device. Following intravenous PCA with fentanyl for analgesia, supplemental analgesics could be given if the patient requested further pain relief, which was explained to the patient and the nursing staff. The first choice was diclofenac sodium (50 mg suppository), and the second choice was pentazocine (15 mg) + hydroxyzine (25 mg) intravenously. The time at which oxygen administration was terminated and oral intake could be started postoperatively was determined by the anesthesiologist based on the patient's state of alertness in the post-anesthesia care unit. After recovery from anesthesia, patients were observed by nursing staff without being informed of their grouping. Resting lumbar pain VAS, lower limb pain VAS, and numbness scores were recorded in the post-anesthesia unit immediately after extubation and in the hospital room at 2, 3, 5, 10, 18, 21, 27, 42, 45, and 51 hours after surgery. Adverse effects such as nausea/vomiting, sedation, dizziness, and dry mouth were recorded as they occurred. Supplemental analgesics used during the 48-hour period were recorded.

2.1. Statistical analysis

A power analysis was performed with reference to a study that investigated whether differences in analgesics used during general anesthesia in spinal surgery lead to differences in postoperative pain.[8] The primary outcome of this study was postoperative pain at rest. A 2-tailed $\alpha = 0.05$ test detecting a difference of 18 ± 20 mm in the pain VAS score between the 2 groups and 80% power required 21 patients in each group (effect size of 0.9). The number of dropouts was about 2 in each group in the report used as reference,[8] and therefore the number of patients required for this study was set at 23 for each group.

Statistical analysis was conducted using SigmaPlot 14.0 (Systat Software Inc., San Jose, CA). The normality of the data distribution was analyzed by the Shapiro–Wilk test. Normally distributed data are presented as mean ± SD and non-normally distributed data are presented as median (interquartile range). Background data were analyzed by the Student's *t* test or Mann–Whitney *U* test for numerical data, and by the chi-square test or Fisher exact test for categorical data (sex, American Society of Anesthesiologists physical status, PLIF level). Numerical data such as resting lumbar pain VAS and lower limb pain VAS were analyzed by 2-way repeated measures analysis of variance followed by the Student's *t* test with Bonferroni correction for group comparisons, while the numbness score and fentanyl consumption were analyzed by the Mann–Whitney *U* test. Supplemental drug use was analyzed by the Fisher exact test. Fentanyl request times and supplemental drug request times were analyzed using the log rank test for survival curves. The incidence of adverse drug reactions was analyzed using the Fisher exact test. $P < .05$ was considered statistically significant.

3. Results

A total of 48 patients were assessed for eligibility for inclusion in the study. Two patients were excluded from enrollment and 46 patients were randomized into 2 groups: the diazepam group (control group) and the duloxetine group. A total of 6 patients (5 in the diazepam group and 1 in the duloxetine group) were lost to follow-up and, therefore, 40 patients completed the study and were included in the final analysis (Fig. 1).

No significant demographic differences were detected between the groups (Table 1). The VAS score at rest in the

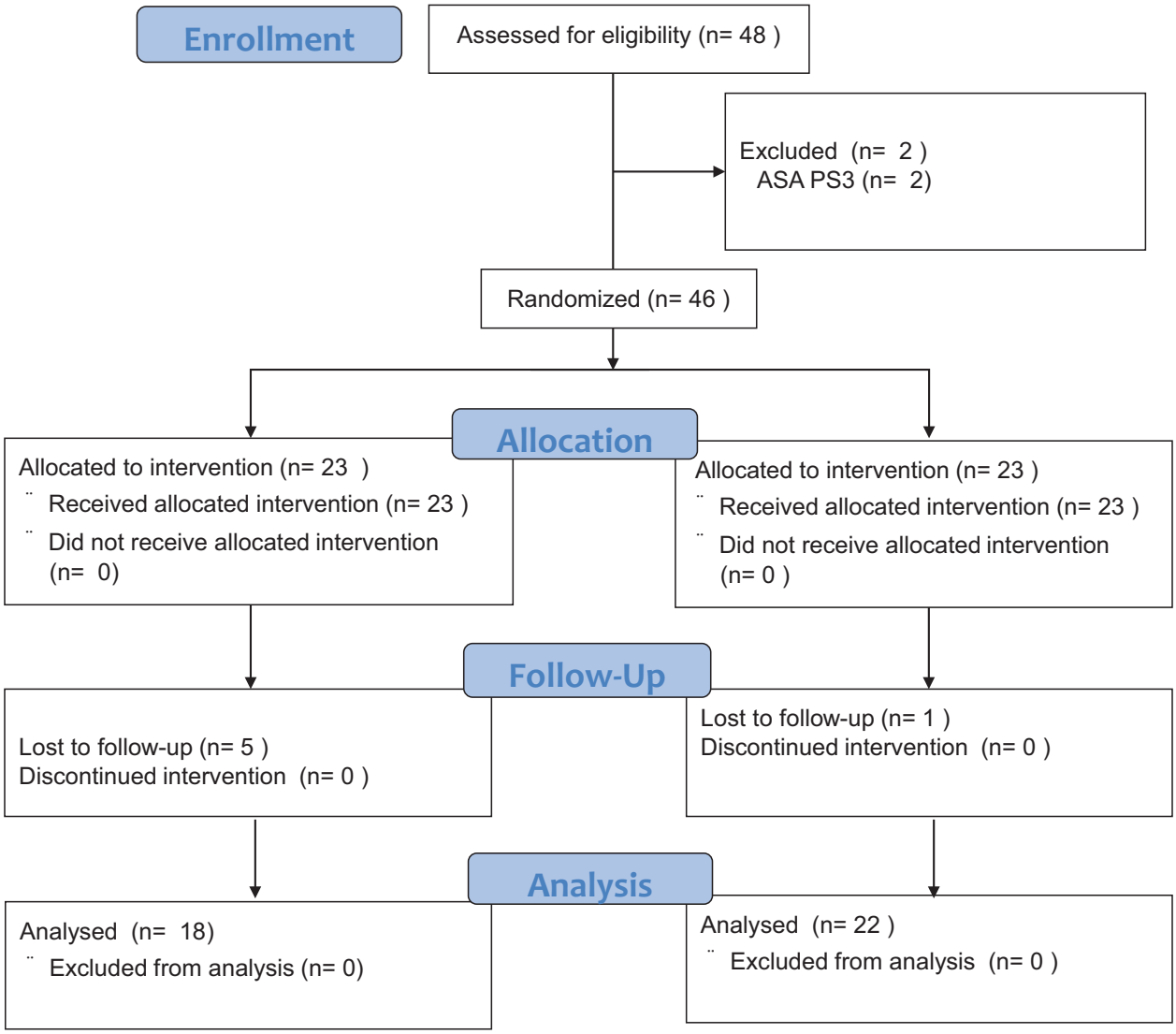

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) participant flow diagram. ASA-PS = American Society of Anesthesiologists physical status.

Table 1

Background data. Normally distributed data are presented as mean ± SD and non-normally distributed data are presented as median (interquartile range).

	Diazepam (n = 18)	Duloxetine (n = 22)	*P*
Age (y)	67.2 ± 10.3	61.8 ± 15.2	.327
Sex (male/female)	10/8	14/8	.152
ASA class (I/II)	7/11	7/15	.627
Height (cm)	157.6 ± 8.0	162.7 ± 12.5	.145
Weight (kg)	62.1 ± 11.8	66.1 ± 12.8	.305
BMI (kg/m^2)	24.8 ± 3.7	24.8 ± 2.5	.932
Duration of surgery (min)	120.8 ± 54.3	107 ± 28.8	.523
Duration of anesthesia (min)	153.1 ± 65.1	152.3 ± 29.7	.775
PLIF level (1/2)	16/2	20/2	1.000
Remifentanil (mg)	1.29 ± 0.44	1.51 ± 0.6	.246
Preoperative low back pain VAS	55.4 ± 23.8	43.0 ± 29.6	.148
Preoperative lower limb pain VAS	70 [50–80]	60 [30–80]	.192
Preoperative numbness (+/–)	13/5	14/8	.812
Preoperative numbness VAS	50 [35–80]	35 [0–70]	.198

ASA = American Society of Anesthesiologists, BMI = body mass index, PLIF = posterior lumbar intervertebral body fusion, VAS = visual analog scale.

lumbar region did not differ between the 2 groups ($P = .192$, Fig. 2). There were significant main effects of time [$F(10, 380) = 18.563$; $P < .001$], but no significant main effects of group [$F(1, 380) = 1.763$; $P = .192$] or a group × time interaction [$F(10, 380) = 0.554$; $P = .851$]. Fentanyl use was compared at 0–12, 12–24, 24–36, 36–48, and 0–48 hours postoperatively;

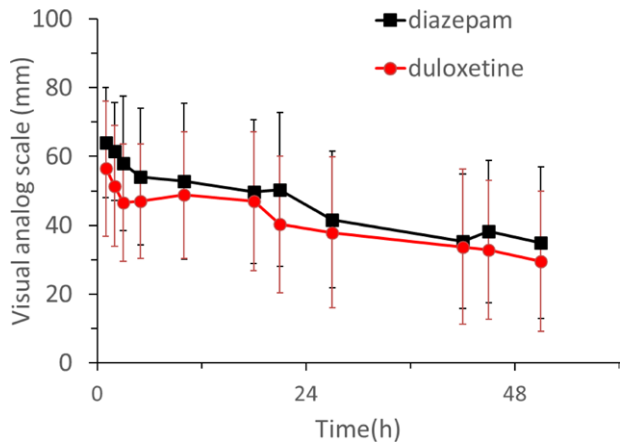

Figure 2. Visual analogue scale score at rest in the lumbar region during the first 51 h after surgery. All data are expressed as the mean ± SD.

no significant difference was detected between the 2 groups ($P = .307$, 0–48 hours, by the Mann–Whitney U test, Fig. 3A). Survival curves are shown for the request times for postoperative intravenous PCA fentanyl administration. Analysis of the first 3 requests showed no significant difference between the 2 groups ($P = .930$, first request time, $P = .831$, second request time, $P = .186$, third request time analyzed by the log rank test for the survival curves, Fig. 3B–D). The rate of supplemental drug use ($P = .638$, by Fisher exact test, Table 2) and the time of the first supplemental drug request ($P = .881$, by the log rank test for the survival curves, Fig. 4) were analyzed, and no significant difference was detected between the 2 groups. The VAS score in the lower limbs at rest did not differ between the 2 groups ($P = .139$, Fig. 5A). There were no significant main effects of group [$F(1, 380) = 2.287$; $P = .139$] or time [$F(10, 380) = 1.650$; $P = .091$] or a group × time interaction [$F(10, 380) = 1.672$; $P = .085$]. The numbness score in the lower limbs was significantly lower in the duloxetine group than in the diazepam group ($P < .05$ at 1, 3, 5, 18, and 51 hours after surgery by the Mann–Whitney U test, Fig. 5B). In Figure 5B, nonparametric tests were performed and thus the results should be presented as box plots, but they are presented as mean ± SD for easier visualization. In all cases, oxygen administration

Table 2

Rate of supplemental drug use.

	Diazepam	Duloxetine	*P*
n	18	22	
Supplemental drug use (%)	44.4	59.1	.638

was terminated and oral intake was started 2 to 3 hours after the patient left the post-anesthesia care unit. In the diazepam group, nausea was observed in 1 patient (5.6%, $P = .450$, by the Fisher exact test). There were no cases of confusion, dizziness, vomiting, or dry mouth.

4. Discussion

In this study, a single preoperative dose of duloxetine (40 mg) did not have analgesic effects against acute postoperative back or lower limb pain in patients undergoing PLIF compared with the control group. Postoperative opioid use and frequency, and the rate and frequency of supplemental drug use also did not differ significantly between groups. On the other hand, a single 40-mg dose of duloxetine administered preoperatively decreased symptoms of lower limb numbness during the acute postoperative period after PLIF. No adverse events were reported in either group.

In the present study, preoperative duloxetine administration had no analgesic effects against acute postoperative pain. Six previous studies[5,6,9–12] included in a meta-analysis[4] reported analgesic effects of perioperative duloxetine at a dose of 60 mg administered 48 hours after surgery. The number of oral administrations ranged from 2 to 7, and the protocols called for duloxetine administration both preoperatively and postoperatively. Several previous studies reported the effect of a single preoperative dose of duloxetine on postoperative acute-phase analgesia. For example, in patients undergoing laparoscopic gynecologic surgery with general anesthesia, 60 mg duloxetine administered preoperatively improved pain at 12 hours postoperatively and reduced opioid use compared with the control group.[13] A single preoperative administration of 60 mg oral duloxetine in patients undergoing major abdominal cancer surgery reduced postoperative pain, decreased opioid consumption, and improved recovery.[14] A study of duloxetine administration at doses of 30, 60,

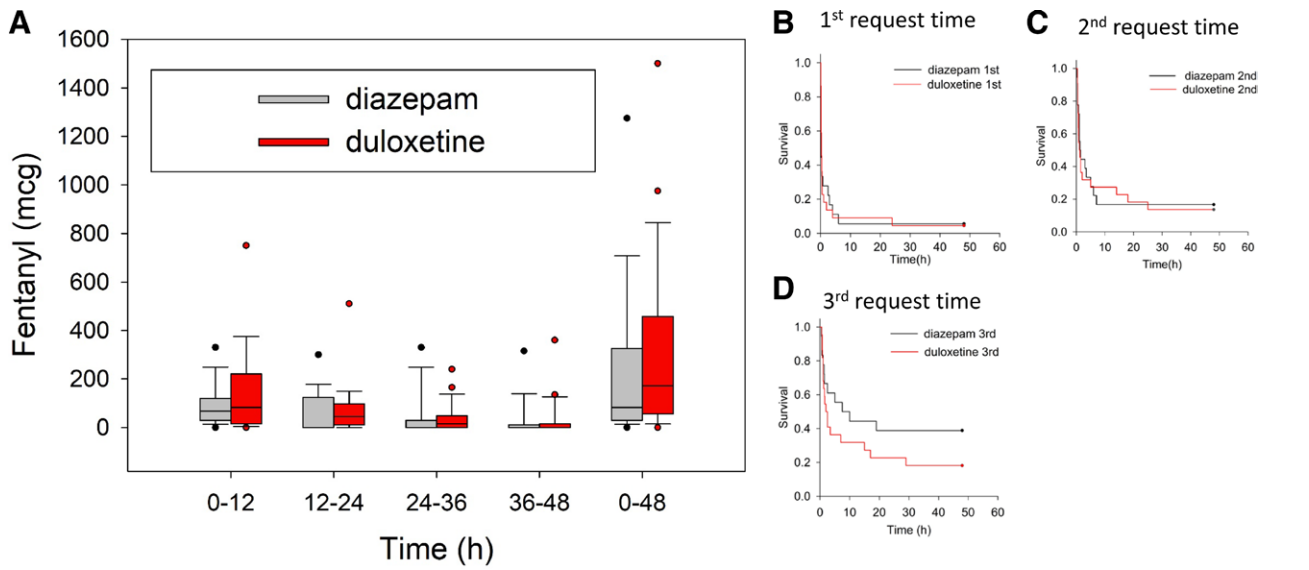

Figure 3. (A) Fentanyl consumption during the first 48 h after surgery. All data are expressed as box plots. (B–D) First to third fentanyl request times during the first 48 h after surgery. All data were analyzed using the log rank test for survival curves.

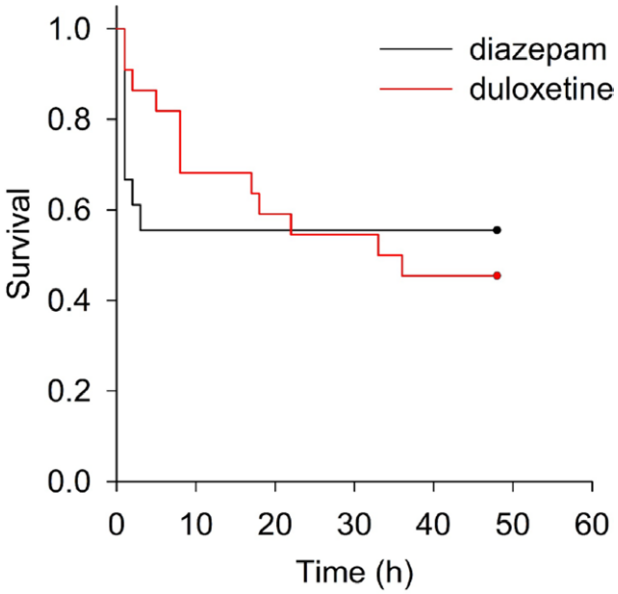

Figure 4. First supplemental drug (diclofenac sodium 50 mg or pentazocine 15 mg + hydroxyzine 25 mg) request time during the first 48 h after surgery. All data were analyzed using the log rank test for survival curves.

and 90 mg given preoperatively to patients undergoing mastectomy reported that 60 mg was the optimal dose with regard to postoperative analgesia and side effects.[15] On the other hand, in a study of patients undergoing total abdominal hysterectomy with spinal anesthesia, preoperative administration of 60 mg of duloxetine did not decrease pain 24 hours after surgery, and the incidence of nausea vomiting and somnolence was higher compared with the control group.[16]

In the present study, a single 40-mg dose of duloxetine was administered preoperatively. Although a previous meta-analysis[4] indicated that perioperative duloxetine administration increases the risk of dizziness, no adverse effects associated with duloxetine administration were observed in this study. Because all patients were instructed to begin oral intake 2 to 3 hours after leaving the post-anesthesia care unit and there was little variation among patients, observations of complications of dry mouth and nausea were not likely affected. Participants in the present study tended to be older than those in previous studies. Complications of postoperative dizziness and drowsiness in older patients increase the risk of postoperative delirium and falls, and should thus be avoided during postsurgical recovery.[17] The dose and frequency of duloxetine administration in our study may not have been sufficient to produce analgesic effects against acute pain, but, on the other hand, no side effects were observed, indicating that the administration protocol was safe.

This study is the first to investigate postoperative analgesia with a single dose of duloxetine administered preoperatively to patients undergoing PLIF surgery. Results of our previous study indicated that a single preoperative oral administration of 150 mg pregabalin reduced acute pain and opioid use after PLIF surgery.[7] In spinal surgery patients, the addition of a single preoperative administration of dexamethasone, pregabalin 150 mg, or their combination to a multimodal analgesic protocol did not improve analgesia over the multimodal analgesic protocol alone.[18] Drugs that are effective for postoperative analgesia and reduce opioid consumption, including their type, frequency of administration, and dosage, are still largely unknown. In contrast to our results, a study comparing the perioperative analgesic effects of multiple administrations of duloxetine and pregabalin in patients with lumbar disc herniation surgery demonstrated that both drugs provided analgesia.[9] Lumbar disc herniation surgery is less invasive than PLIF, which may account for the difference in the results; in addition, we evaluated a single preoperative administration.

A single 40-mg dose of duloxetine administered preoperatively decreased symptoms of lower limb numbness during the acute postoperative period after PLIF. There are no previous reports of perioperative duloxetine administration improving perioperative lower limb numbness during the acute postoperative period after PLIF. Patients with lumbar spinal root compression in PLIF often experience preoperative limb numbness, which may be exacerbated by manipulations of the spinal cord or surrounding nerves during surgery.

The mechanisms underlying the improvement in limb numbness symptoms during the acute postoperative period are not clear. Numbness is a typical symptom of neuropathic pain, and the potential effects of duloxetine administration to increase noradrenaline in the dorsal horn of the spinal cord[19,20] may improve neuropathic pain-like symptoms.

This study has some limitations. Postoperative lower limb numbness symptoms were evaluated using the numbness score. Because numbness symptoms were assessed preoperatively using the VAS, it is difficult to compare preoperative and postoperative numbness symptoms. In addition, because spinal cord decompression was performed during surgery, the effect of surgery on improving numbness symptoms must be taken into consideration. To the best of our knowledge, no previous studies have compared early postoperative pain with PLIF in 2 groups of patients taking preoperative medications. We performed a power analysis based on a study of PLIF in which the primary outcome was to compare early postoperative pain between 2 groups.[8] The protocol of the study used for the power analysis differed from that of our study. The present study may have

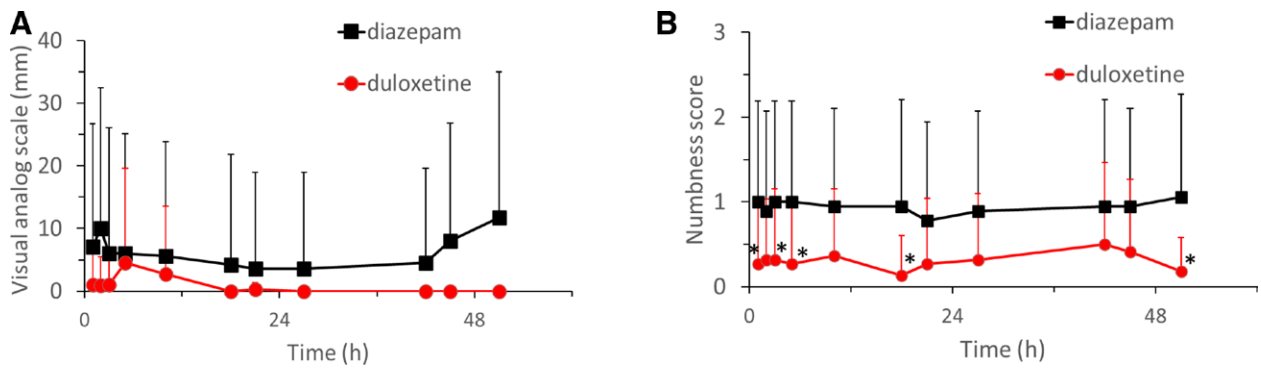

Figure 5. (A) Visual analogue scale score at rest in the lumbar region during the first 51 h after surgery. All data are expressed as the mean ± SD. (B) The numbness score in the lower limbs during the first 51 h after surgery. Because nonparametric tests were performed, the results should be presented as box plots, but for easier visualization, they are presented as mean ± SD. *$P < .05$ by the Mann–Whitney U test.

been underpowered given that the final analysis included only 40 patients in contrast to the estimated 42 patients required to provide a power of 80%.

In summary, a preoperative single administration of 40 mg duloxetine did not improve postoperative PLIF pain and opioid use, but improved symptoms of lower limb numbness postoperatively. Duloxetine may reduce postoperative neuropathic pain-like symptoms after PLIF.

Author contributions

Acquisition of data: Nao Fujita, Hideo Suzuki, Noboru Tsukamoto.
Administrative, technical, or material support: Hideo Suzuki, Noboru Tsukamoto.
Analysis and/or interpretation of data: Tadanao Hiroki, Takashi Suto, Jo Ohta, Hideaki Obata.
Concept and design: Tadanao Hiroki, Nao Fujita, Hideaki Obata.
Critical revision of the manuscript for important intellectual content: All authors.
Drafting of the manuscript: Tadanao Hiroki.
Statistical analysis: Tadanao Hiroki, Hideaki Obata.
Supervision: Shigeru Saito.

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