

Clinical Study

Intraoperative systemic infusion of lidocaine reduces postoperative pain after lumbar surgery: a double-blinded, randomized, placebo-controlled clinical trial

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Abstract

BACKGROUND CONTEXT: Analgesic effect of lidocaine infusion on postoperative pain.

PURPOSE: The aim of this study was to evaluate the analgesic effect of lidocaine infusion on postoperative pain after lumbar microdiscectomy.

STUDY DESIGN: This study used a prospective, randomized, double-blinded, and placebo-controlled clinical trial.

PATIENT SAMPLE: Fifty-one patients participated in this randomized, double-blinded study.

OUTCOME MEASURES: The primary outcome was the visual analog scale (VAS) (0–100 mm) pain score at 4 hours after surgery. The secondary outcomes were the VAS pain score at 2, 8, 12, 24, and 48 hours after surgery, the frequency with which patients pushed the button (FPB) of the patient-controlled analgesia system, and the fentanyl consumption at 2, 4, 8, 12, 24, and 48 hours after surgery. Other outcomes were satisfaction scores regarding pain control and the overall recovery process, incidence of postoperative nausea and vomiting (PONV), and length of hospital stay (HS).

METHODS: Preoperatively and throughout the surgery, Group L received intravenous lidocaine infusion (a 1.5-mg/kg bolus followed by a 2-mg/kg/h infusion until the end of the surgical procedure) and Group C received normal saline infusion as a placebo.

RESULTS: The VAS scores and fentanyl consumption were significantly lower in Group L compared with Group C except at 48 h after surgery ($p < .05$). Total fentanyl consumption, total FPB, length of HS, and satisfaction scores were also significantly lower in Group L compared with Group C ($p < .05$).

CONCLUSIONS: Intraoperative systemic infusion of lidocaine decreases pain perception during microdiscectomy, thus reducing the consumption of opioid and the severity of postoperative pain. This effect contributes to reduce the length of HS. © 2014 Elsevier Inc. All rights reserved.

Keywords:

Inflammation; Lidocaine; Microdiscectomy; Muscle injury; Opioid consumption; Postoperative pain

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EVIDENCE & METHODS

Context

Minimizing postoperative pain without increasing risks is a common goal for surgeons. The authors report their experience with intraoperative systemic lidocaine.

Contribution

In this RCT, they found that the lidocaine group reported less pain and used less fentanyl postoperatively compared to placebo group. The lidocaine group also went home earlier, although the local standard of care in this aspect is not generalizable.

Implications

The findings are interesting but further study is indicated. While a power analysis was undertaken, the numbers were generated using a very small pilot that did not demonstrate clinically significant difference in pain response. There are many confounding factors (eg, patient variables, intraoperative difference) that can impact reported pain and PCA usage. Furthermore, it is unclear whether this small trial is powered adequately to answer the question, as it pertains to both efficacy and safety.

—The Editors

Introduction

The main goal of lumbar discectomy surgery is to relieve pain, but the surgery itself, ironically, induces postoperative pain. Most patients experience postoperative back pain after lumbar surgery, resulting in longer hospital stays (HSs) and a delayed return to normal activity. To relieve postoperative pain, potent narcotics or analgesics have to be used, which can lead to complications, such as delirium, nausea, vomiting, respiratory depression, and so on. Therefore, it is desirable to reduce the use of narcotics or analgesics in the postoperative period.

Lidocaine is a well-known local anesthetic, and it has been shown to have anti-inflammatory and anti-ischemic effects in some cases, although not all [1–7]. Additionally, postoperative pain is connected to a variety of mechanisms, such as pain perception, inflammation, muscle spasm, bowel distension, and tissue ischemia; and the main mechanism varies according to the tissue. For this reason, results demonstrating the relationship between intravenous (IV) lidocaine and postoperative pain are often contradictory [1,8–10]. For example, Cassuto et al. [1] reported that low-dose continuous infusion of lidocaine could reduce the severity of postoperative pain in cholecystectomy patients. In contrast, Insler et al. [10] showed that continuous infusion of low-dose lidocaine did not significantly decrease the need for supplemental narcotic analgesics after coronary artery bypass surgery. In 2007, Herroeder et al. [3] reported that perioperative systemic lidocaine not only

improved gastrointestinal motility, but also significantly shortened the length of HS. However, although systemic lidocaine decreased inflammatory reaction in Herroeder et al. [3] study, it did not significantly reduce postoperative pain. Thus, the benefit of systemic lidocaine is controversial, and the effect could be different in various organs.

To the best of our knowledge, this was first clinical trial of systemic lidocaine for spinal surgery. The aim of this study was to evaluate the analgesic effect of lidocaine infusion on postoperative pain after lumbar microdiscectomy.

Methods

The study protocol was approved by the institutional review board at our hospital and the study was registered in the ClinicalTrials.gov Protocol Registration System (NCT01319682). This study was carried out according to the principle of the Declaration of Helsinki 2000, and written informed consent was obtained from all the participants before inclusion in the trial.

Subjects

All the patients undergoing elective one-level laminectomy and discectomy under general anesthesia between March 2011 and April 2012 were assessed for study eligibility. Inclusion criteria were the presence of a lumbar disc herniation on magnetic resonance imaging and persistent radiating pain in the leg after 6 weeks of conservative treatment. Patient ages ranged from 40 to 60 years. The exclusion criteria were patients who weighed less than 45 kg or more than 100 kg; had a history of prior spinal surgery at the same level; had severe underlying respiratory, renal, hepatic, or cardiologic disease; or had a history of allergic reactions to local anesthetics. Further exclusion criteria were evidence of previous opioid usage or a psychiatric medical history. The decision to enroll or exclude patients was made by the investigator, who did not otherwise participate in conducting the study and data collection.

Study design and randomization

We performed a randomized, double-blind, placebo-controlled study. Randomization into one of the two groups was based on a random table generated using an R-program. Block randomization with a block size of four or six and equal allocation was used to prevent imbalances in treatment assignments. The randomization sequence was generated by a statistician who was not involved with the study. The details of the series were unknown to the investigators, and the group assignments were kept in sealed envelopes, each bearing only the case number on the outside. After admitting the patient into the operating room and just before the induction of anesthesia, a numbered envelope was opened and the card inside determined to which group the patient was assigned. To keep the

anesthesiologist “blind” to the patients’ assigned group, the patients were given lidocaine or normal saline without labels. Preparation of the bolus and continuous infusion was arranged by an additional investigator reading the card. Patients assigned to Group L received an IV bolus injection of 1.5 mg/kg lidocaine followed by a continuous infusion of 2 mg/kg/h; Group C received the same amount of normal saline injection as a placebo.

All parties involved, including the patients, the surgeon, the anesthesiologists, and the investigator preparing drugs and collecting data were unaware of the study drugs or the patients’ group assignment, with the exception of the study coordinator (HK). The study coordinator was responsible for maintaining the flow of the study.

General anesthesia

All patients received the same anesthetic protocol. The patients did not receive premedication, and anesthesia was induced with 5 mg/kg of thiopental IV and 0.6 mg/kg of rocuronium IV. Anesthesia was maintained using 2% to 3% sevoflurane in 1.5 L/min nitrous oxide (N₂O), and 1.5 L/min O₂. The noninvasive arterial blood pressure, electrocardiography, and pulse oximetry were monitored continuously. During surgery, the patients received an IV infusion of lactated Ringer solution at a rate of 5 to 10 mL/kg/h. No additional analgesics were injected during the surgery.

Microdiscectomy procedure

Surgery was performed by one surgeon (Y-BK) using a previously described microdiscectomy technique [11]. Briefly, a 3.0-cm-sized vertical skin incision was made. The underlying muscles were dissected with a No. 10 and 15 blade, and the affected lamina was exposed. A partial laminectomy was done, and the herniated disc material was removed.

Postoperative pain control

To control postoperative pain, IV patient-controlled analgesia (PCA) (Automed 3300; Ace Medical Co., Seoul, South Korea) was used to administer fentanyl. Preoperatively, the patients were instructed on the use of the PCA. Fentanyl infusion involved (1) an automatic, continuous infusion of 0.1 µg/kg/h (total regimen of 100 mL) of fentanyl and (2) a 0.1-µg/kg bolus with a lockout interval of 15 minutes, when the patient self-administered it.

In the case of persistent pain exceeding a visual analog scale (VAS) score of 30 mm, an additional 50 µg of fentanyl was IV injected by an investigator until the pain was relieved to a level falling below a VAS pain score of 30 mm.

Data collection

The primary outcome was the VAS (0–100 mm) pain score at 4 hours after surgery. The secondary outcomes were the VAS pain score at 2, 8, 12, 24, and 48 hours after surgery;

the frequency that patients pushed the button (FPB) of the PCA system; and the fentanyl consumption at 2, 4, 8, 12, 24, and 48 hours after surgery. Other outcomes were satisfaction scores regarding pain control and the overall recovery process, incidence of postoperative nausea and vomiting (PONV), and the length of HS. The values of white blood cell (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), creatine kinase MM (CPK-MM), and lactate dehydrogenase-5 (LDH-5) were also measured preoperatively and at postoperative days 1, 3, and 5. All outcome assessments were done by two investigators blinded to the study.

During the preoperative visit, the patients were instructed on the use of the 100-mm VAS (0=“no pain” and 100=“worst pain imaginable”) for pain assessment, and the use of the PCA device. Two investigators who were responsible for data collection during the study were also instructed on the use of the VAS and the PCA device, and a protocol for instruction on their use was provided. Age, American Society of Anesthesiologists (ASA) physical status, duration of anesthesia (from injection of thiopental to extubation), and duration of surgery (from skin incision to end of closure) of each patient were determined and recorded. To measure pain intensity, the VAS pain score was measured at 2, 4, 8, 12, 24, and 48 hours after surgery. The FPB for PCA and fentanyl consumption (the sum of additional IV fentanyl bolus injections and the fentanyl delivered by the PCA system) were evaluated at similar time periods: up to 2, 2 to 4, 4 to 8, 8 to 12, 12 to 24, and 24 to 48 hours after surgery. Satisfaction scores regarding pain control and the overall recovery process were obtained at 48 hours after surgery (using a numeric rating scale from 0=“very dissatisfied” to 10=“very satisfied”). Incidences of PONV were recorded for all patients up to 48 hours after surgery. We considered it PONV if patients felt any nausea or had any vomiting.

Further, the length of HS was collected from each patient. Hospital stay was determined by the number of days from admittance to discharge. Discharge criteria included ability to self-ambulate or self-care, no signs of wound problems, absence of infectious signs or increased infection parameters, and pain controlled by oral analgesics.

We evaluated inflammatory factors (WBC, ESR, CRP) and muscle enzymes (creatine kinase MM [CPK-MM], lactate dehydrogenase-5 [LDH-5]) at same time (8 AM) of admission and 1, 3, and 5 days postoperatively. Blood samples were taken by neurosurgical unit nurses, and they were blinded to this study.

Statistical analysis

The primary outcome variable was the VAS pain score, which was measured at 4 hours after surgery. To estimate the required sample size, a pilot study was conducted by measuring VAS after surgery on 10 patients receiving IV normal saline or lidocaine. The VAS scores at 4 hours after surgery in Groups C and L were 31.0 ± 13.0 and 20.0 ± 11.7 ,

respectively. We wanted to demonstrate a difference of 10 mm in the VAS pain score at 2 hours after surgery between the groups. With a two-tailed $\alpha=0.05$ and a power of 80%, we needed 24 patients in each group. Considering a loss-to-follow-up rate of 10%, we decided to ask 54 patients to participate in the study.

We used an intention to treat strategy, that is, all participants were analyzed as randomized irrespective of whether they had completed the study. Missing data were completed using a last observation carried forward analysis. Association among VAS, FPB, and fentanyl consumption were analyzed using an as-treated strategy.

For intergroup comparisons, the distribution of the data was first evaluated for normality using the Kolmogorov-Smirnov test. The normally distributed data were presented as the mean $\pm$ standard deviation and the groups were compared via the Student *t* test. The non-normally distributed data were expressed in medians (interquartile range) and these data were analyzed via the Mann-Whitney *U* test.

Descriptive variables were subjected to χ^2 analysis or Fisher exact test, as appropriate, and *p* values less than

.05 were regarded as statistically significant. The data in the figures were reported as the mean $\pm$ standard error. Statistical analysis was conducted using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Data demographics

Of 66 patients assessed for eligibility, 12 patients did not meet the inclusion criteria. Of 54 patients asked to participate in the study, 3 patients declined to participate in the study. Of the 51 patients included, 26 were randomized to Group C and 25 to Group L. Four patients dropped out during the study. Three patients in Group C and one in Group L were treated by other pain killers, because of PONV that was unresponsive to antiemetic treatment and likely induced by fentanyl injection (Fig. 1). There were no significant differences between the two groups with respect to age, height, weight, gender, ASA class, and duration of operation time (Table 1).

CONSORT 2010 Flow Diagram

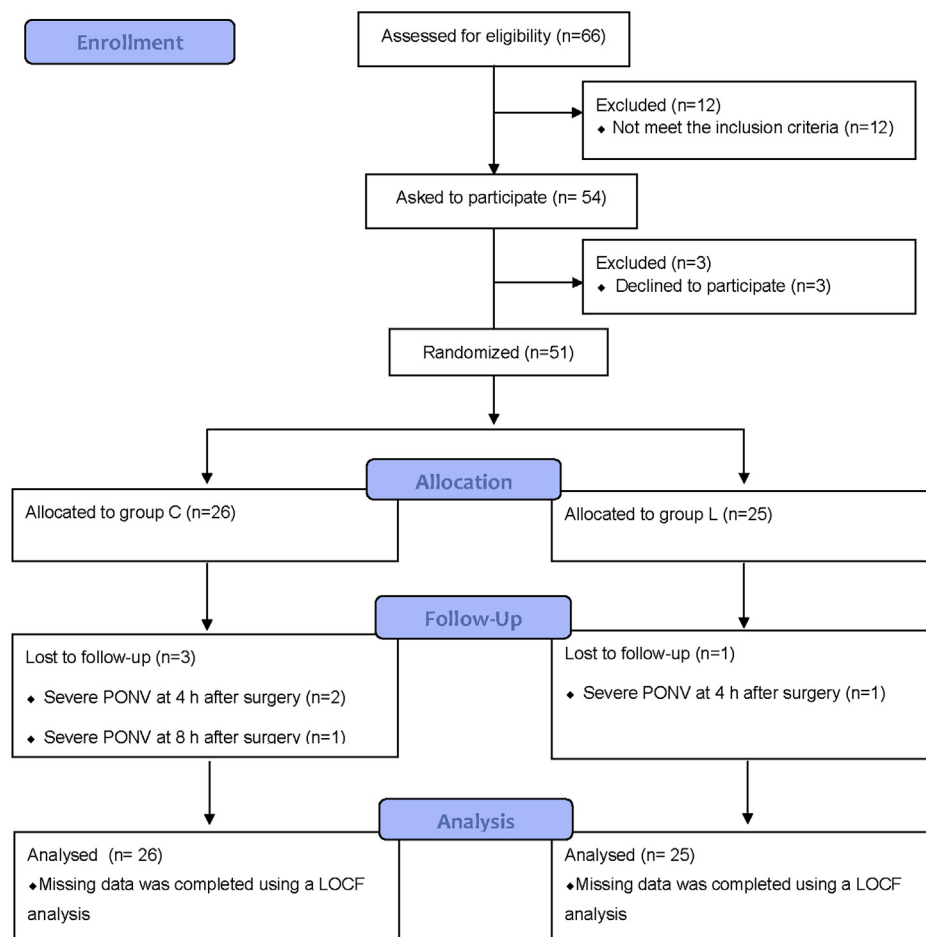


Fig. 1. Study design according to the CONSORT 2010 flow diagram. LOCF, last observation carried forward; PONV, postoperative nausea and vomiting.

Table 1
Demographics and preoperative variables

Variables	Group C, n=26	Group L, n=25
Age, y*	48.00 (41.00–56.00)	52.00 (44.50–57.50)
Gender M/F, n	8/18	13/12
ASA I/II/III, n	5/19/2	3/19/3
Height, cm	159.19±8.41	160.76±8.08
Weight, kg	64.62±9.50	65.05±7.08
BMI, kg/m ²	25.46±3.01	25.22±2.68
Duration of OP*	107.50 (55.00–135.00)	110.00 (80.00–140.00)
Pre OP VAS	42.27±7.25	41.84±8.39
Pre OP Analgesic, Yes/No, n	20/6	19/6

ASA, American Society of Anesthesiologists physical status; BMI, body mass index; F, female; M, male; n, number of patients; OP, operation; VAS, visual analog scale.

Note: Values are expressed as mean±standard deviation, median (Q25–Q75), or absolute number.

* Mann-Whitney U test is used and expressed as median (Q25–Q75) because of abnormal distribution.

Pain intensity, opioid consumption, and side effects of the drug

VAS levels were significantly higher in Group C compared with Group L up to 24 hours after surgery (Fig. 2). In both groups, the VAS pain score was highest at 2 hours and gradually diminished during the time sequence.

The FPB was significantly higher in Group C than in Group L until 12 hours. In terms of overall FPB, which was measured up to 48 hours after surgery, Group C also showed a higher FPB value compared with Group L (Table 2). Postoperative fentanyl consumption from PCA and rescue analgesia was higher in Group C, when compared with Group L, up to 24 hours, and decreased gradually in both groups ($p<.05$) (Fig. 3). In terms of the total amount of injected fentanyl, Group L required significantly less analgesia than did Group C ($p<.001$) (Table 2). Satisfaction score was higher in Group L than Group C ($p<.05$) (Table 2). Nausea and vomiting were less frequent in Group

L compared with Group C, but the differences were not statistically significant. There were no side effects from the lidocaine, such as arrhythmia, hypotension, and hypersensitivity.

Length of HS

With respect to length of HS, there were significant differences between the two groups ($p=.039$) (Table 2). On average, patients in Group L were discharged 1 day earlier than those in Group C.

Inflammatory factors and muscle enzymes

WBC, ESR, and CRP are represented in Table 3. The values of WBC and ESR were not significant differences between the two groups, but measurement of CRP showed significant difference at POD 3 ($p=.046$) (Fig. 4, Left).

CPK-MM and LDH-5 also increased after surgery in the both groups. Especially, the CPK-MM level was significantly higher in Group C compared with Group L at POD 3 and 5 ($p<.05$) (Fig. 4, Right).

Discussion

The aim of this study was to evaluate the analgesic effect of lidocaine infusion on postoperative pain after lumbar microdiscectomy. Intraoperative systemic infusion of lidocaine significantly reduced postoperative pain for up to 48 hours, and fentanyl consumption for up to 24 hours, after surgery. Also, patients undergoing systemic lidocaine infusion gave higher satisfaction scores of the overall recovery process, which included their assessment of pain control. As a result, there was a reduction in the length of HS for patients in the lidocaine group.

The underlying mechanisms to explain this might be multifactorial. However, prevention of central hyperalgesia seems to be one of the contributors. Pain impulses from an injured area are carried to the central nervous system by afferent A-delta and C-fibers [12], and lidocaine blocks voltage-sensitive sodium channels responsible for the generation of ongoing activity in these neurons [4,13]. Furthermore, monoethylglycinexylidide, which is the major metabolite of lidocaine, may play an antinociceptive role by inhibiting glycine uptake, even with a low serum dose [14]. Preemptive analgesia is the process of preventing pain by initiating pain-relief treatment before surgery trauma. This process involves administration of local anesthetics, opioids, and nonsteroidal anti-inflammatory drugs via local, epidural, intrathecal, or systemic routes [15–17]. Especially, systemic administration of lidocaine should prevent central hyperalgesia and reduce postoperative pain [1,15,17–19].

Another hypothesis to explain our overall result involves the muscle protective effect of lidocaine during microdiscectomy. Ischemic damage is one of the muscle injury mechanisms during microdiscectomy [20–22]. Lidocaine has beneficial effects on limiting ischemic or reperfusion damages [2,5,23–25]. However, the impact of muscle injury

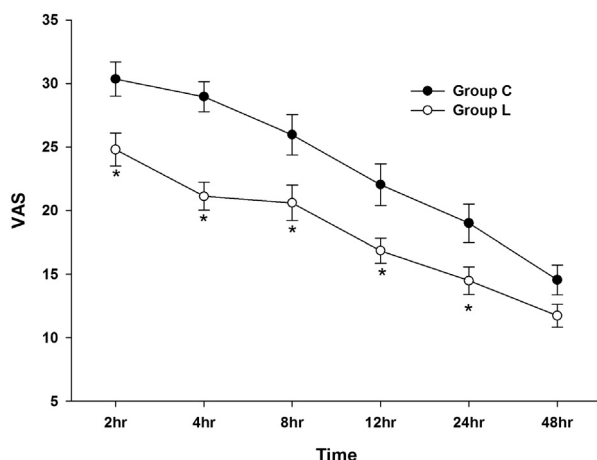


Fig. 2. Visual analog scale (VAS) pain score after lumbar surgery. Data are mean±standard error. *Difference between two groups was statistically significant ($p<.05$).

Table 2
Postoperative variables

Variables	Group C, n=26	Group L, n=25	Difference between groups (95% CI)	p Value
Total FPB	35.5 (24.50–46.50)	21.0 (13.00–25.50)	18.20 (8.32–28.09)	<.001 ^{*,†}
Total fentanyl	810.63±169.24	596.08±136.35	214.55 (127.86–301.24)	<.001 [†]
Nausea	8/18	4/21	0.15 (–0.08 to 0.36)	.214
Vomiting	5/21	2/23	0.11 (–0.09 to 0.31)	.419
Length of HS	7.0 (4.75–11.25)	6.00 (3.50–7.50)	–2.05 (–3.82 to –0.27)	.039 ^{*,†}
Satisfaction score	6.0 (5.00–7.00)	7.00 (6.00–8.00)	0.78 (0.31–1.52)	.045 ^{*,†}

CI, confidence interval; FPB, frequency to push the button of patient-controlled analgesia system; HS, hospital stay; n, number of patients.

Note: Values are expressed as mean±standard deviation, median (Q25–Q75), or absolute number.

* Mann-Whitney *U* test is used and expressed as median (Q25–Q75) because of abnormal distribution.

† <.05 compared with Group C.

on postoperative back pain is less clear, but several reports suggested that muscle damage during lumbar surgery might be related to postoperative back pain [22,26]. Shin et al. [26] reported that the microendoscopic technique could reduce iatrogenic muscle damage (CPK-MM at POD 3 and 5) and postoperative pain at POD 1 and 5. In Kotil et al.'s [22] study, discectomy with continuous retraction increased the CPK serum level, iatrogenic muscle damage, and postoperative pain at POD 1 compared with lumbar discectomy with intermittent reaction release. These results suggest that muscle damage might be related to the postoperative back pain. We found the CPK-MM level in Group C was significantly higher than Group L at POD 3 and 5 ($p<.05$) (Fig. 4, Right).

Lidocaine is widely reported to have anti-inflammatory properties [1,3,5,9,25,27]. Additionally, inflammatory reaction is an important mechanism of reperfusion injury in heart and skeletal muscles [5,27,28]. Therefore, lidocaine seemed to be an ideal candidate strategy to attenuate reperfusion injury [6,7,27,29,30]. In our study, however, we found statistically significant differences between the groups only in CRP changes at POD 3 (Fig. 4, Left). Of

course, this result cannot confirm the anti-inflammatory effects of lidocaine in general. Additionally, CRP is produced by the liver and rises when there is inflammation throughout the body, so this result should be read cautiously. Fortunately, there were no postoperative infections in our study, and CRP is used mainly as a marker of inflammation. Measuring CRP values is useful in determining inflammation reaction after surgery [31,32], so this result was inconclusive as to whether lidocaine has an anti-inflammatory effect.

The length of HS is an important result of our study. Lidocaine shortened the length of HS by 1 day for patients undergoing lumbar surgery. Effective postoperative pain control is associated with lower rates of morbidity and mortality, and also results in shorter length of HS, which reduces overall costs [33]. In the present study, intraoperative systemic infusion of lidocaine reduced postoperative pain for up to 48 hours, and might consequently contribute to increased physical activity after surgery. These effects contribute to shorten the length of HS.

Systemic lidocaine can induce allergic reaction, arrhythmia, hypotension, drowsiness, or convulsions [34]. Many

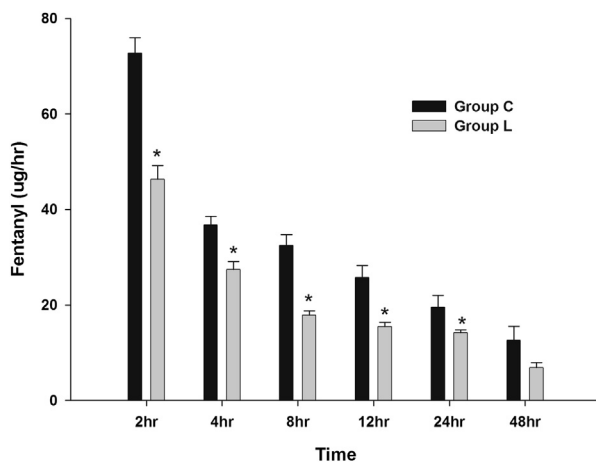


Fig. 3. The fentanyl consumption after lumbar surgery (the sum of additional intravenous fentanyl bolus injections and the fentanyl delivered by the patient-controlled analgesia system). Data are mean±standard error. *Difference between two groups was statistically significant ($p<.05$).

Table 3
Effects of lidocaine on inflammatory factors

Factors	Group C, n=26	Group L, n=25	p Value
WBC, 10 ⁹ /L			
Preoperative	6.59±2.26	7.45±2.84	.260
POD 1	9.86±3.15	9.57±3.40	.754
POD 3	9.04±2.36	9.79±2.65	.294
POD 5	7.12±2.64	7.36±2.22	.740
ESR, mm/h			
Preoperative	23.64±14.51	22.12±15.09	.718
POD 1	23.56±19.33	25.84±18.24	.958
POD 3	37.80±21.22	33.76±21.38	.506
POD 5	42.64±20.43	39.28±25.25	.607
HS-CRP, IU/L			
Preoperative	2.58±8.97	2.58±8.97	.999
POD 1	36.50±30.31	35.70±31.79	.928
POD 3	90.84±48.54	62.08±50.85	.046
POD 5	34.04±23.48	24.50±22.85	.152

ESR, erythrocyte sedimentation rate; HS-CRP, high sensitivity C-reactive protein; POD, postoperative day; WBC, white blood cell count.

Note: Values are expressed as mean±standard deviation.

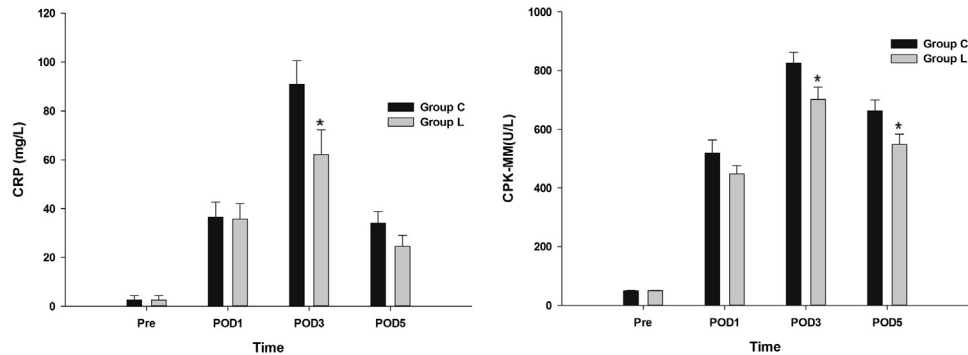


Fig. 4. Changes in C-reactive protein (CRP) and creatine kinase MM (CPK-MM) after microdiscectomy. Values are expressed as mean $\pm$ standard error. (Left) CRP, (Right) CPK-MM. *Difference between two groups was statistically significant ($p < .05$).

studies show IV lidocaine with a 1.5-mg/kg bolus and a 2.0-mg/kg/h infusion dose as safe and without side effects. Even a larger dose and longer duration of administration of lidocaine did not reach toxic concentrations or have side effects [35,36]. Further, to prevent possible complications, we observed patients precisely for 2 to 3 hours (the elimination half-life of lidocaine is approximately 90 to 120 minutes [37]) after surgery.

There are some limitations of the present study. We did not check the plasma concentration of lidocaine. The check on plasma concentration would have improved the understanding of the relationship between the pharmacokinetics of this drug and its systemic and side effects. The second limitation is that we did not analyze muscle pressure during surgery. It could influence paraspinal muscle injuries [38], but surgery was done using the same retractor system by one neurosurgeon (Y-BK). Third, none of our patients had a severe underlying disease. Therefore, the results of our study should not be generalized to other patients with severe underlying diseases.

Conclusions

Intraoperative systemic infusion of lidocaine decreases pain perception during microdiscectomy, thus reducing the consumption of opioids and the severity of postoperative pain. This effect contributes to reduce the length of HS. Additionally, systemic lidocaine infusion may reduce muscle damage and inflammatory reaction, although future research would be needed to support this conclusion.

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