Original Article

Intravenous Lidocaine Infusion with Single Low-Dose Ketamine as an Adjuvant to General Anesthesia in Posterior Spine Fusion

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Abstract

Background: Posterior spinal fusion (PSF) is used to correct degeneration of the lumbar spine with considerable postoperative pain. We aimed to compare the total intraoperative and postoperative opioid consumption and numeric pain scale between the lidocaine/ketamine group and the narcotic-only group.

Materials and Methods: Sixty adult patients (age 18–65 years) planned for elective PSF were included. Patients were randomly allocated into the lidocaine/ketamine group (LK group), who received lidocaine and ketamine injection and usual perioperative narcotic analgesia, and the narcotic-only group (N group), who depended on the N narcotics only. The primary outcome measures were total intraoperative and postoperative opioid consumption and pain scores during the first 24 hours postoperatively. The secondary outcome measures included sedation score, intravenous rescue analgesia, pruritis, and postoperative nausea and vomiting during the first 24 hours postoperatively.

Results: Patients in the LK group had lower intraoperative fentanyl consumption (216.3±28.8 µg) than those in the N group (363±35 µg). The LK group consumed less morphine in the first 24 hours following surgery (49.5±6.0 mg) than the N group (57.8±8.6 mg). The LK group reported reduced pain scores at all-time intervals during the first 24 hours (2, 6, 12, and 24 hours) than the N group did.

Conclusion: Intraoperative lidocaine infusion combined with low-dose ketamine reduced narcotic consumption and pain scores in patients undergoing PSF.

Keywords: Narcotic, Ketamine, Lidocaine, Patient-controlled, Analgesia, Spine fusion

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Introduction

Numerous techniques have been tried to control postoperative pain, mainly administering opioids via the intravenous, intrathecal, or epidural routes (1). A significant dose of opioids is required to provide adequate perioperative analgesia, which leads to a wide range of adverse effects (2). These negative effects will increase patients' morbidity with subsequent increases in the in-hospital stay. Therefore, satisfactory postoperative analgesia is crucial to enable early ambulation and hospital discharge and avoid the onset of chronic pain (3).

Posterior spinal fusion (PSF) is usually associated with considerable postoperative pain because of the extensive skin, subcutaneous tissues, ligaments, and bone dissection and the mechanical irritation and compression applied to the spine (4). To decrease opioid consumption, the best practice is to use multiple analgesics with different mechanisms of action (5).

Intravenous lidocaine has been considered a good choice of adjuvant analgesic as it has analgesic, anti-inflammatory, and antihyperalgesic properties (6). In addition, intravenous lidocaine is relatively safe, inexpensive, and easily administered. Some authors have suggested that the antinociceptive properties of systemic lidocaine may be the result of a reduction in surgical stimulation (7). The exact mechanism through which systemic lidocaine exerts its analgesic result remains unidentified, usually other than the recognized sodium channel blockade effect (8). Some possible tools include the direct inhibitory action of lidocaine on N-methyl-D-aspartate (NMDA) receptors and some potassium and calcium channels (9). Furthermore, intravenous lidocaine may immediately stimulate opiate receptors (10).

Recently, the popularity of low-dose ketamine has increased for acute perioperative pain management (11). The analgesic property of ketamine is mainly due to the blockage of the NMDA receptors (12). Therefore, antagonists of the NMDA receptor, such as ketamine, can inhibit the spread of nociceptive impulses to the brain (13). Ketamine inhibits nociceptive neurons in the dorsal horn and activates descending inhibitory pathways from the supraspinal areas (14).

Ketamine can be administered by multiple routes, including intravenous (IV) bolus injection, continuous IV infusion, epidural route, and even wound infiltration (15). A bolus dosage of ≤ 0.5 mg/kg or an IV infusion rate of ≤ 1 mg/kg/h is defined as IV low-dose ketamine (16).

Although there have been numerous reports on the use of lidocaine and ketamine to enhance postoperative analgesia, the novelty of this research may arise from the fact that no studies have evaluated the combination of both drugs.

We hypothesized that in patients undergoing PSF, a multimodal regimen that includes an IV lidocaine infusion with IV low-dose ketamine would be more beneficial with better and long-lasting analgesia and fewer adverse effects than a narcotic-only regimen.

Methods

This trial was carried out in the assembled operating theater of Ain Shams University educational hospital, following the Helsinki declaration-2013, between March and October 2021. All of the patients participating in the trial signed an informed consent form. The protocol for the study was approved by the Faculty of Medicine, Ain Shams University Local Ethical Committee (FMASU R 87 / 2021).

Sixty adult patients, ranging in age from 18 to 65 years, who underwent two or more levels of elective lumbar PSF under general anesthesia were enrolled. Inclusion criteria were patients of both sexes with a body mass index <35 and an American Society of Anesthesiologists (ASA) physical status I/II.

Exclusion criteria comprised a history of hypersensitivity to lidocaine or ketamine, pregnancy, severe renal disorder, hepatic dysfunction, cardiac arrhythmias, severe cardiac or pulmonary disease, increased intraocular pressure, history of psychiatric disorders, epilepsy, history of alcohol or drug abuse, patients receiving beta-blockers or antiarrhythmics, uncontrolled diabetes or hypertension, and patients who are unable to use patient-controlled analgesia (PCA) pump.

The Pan African Clinical Trials Registry was used to register the trial prospectively (PACTR; trial No. PACTR202103785412583).

Using a computer-generated random table, patients were allocated to either the narcotic-only group (N group or control group), in which patients depended on narcotics only (including fentanyl and morphine) for intraoperative and postoperative pain control or the lidocaine/ketamine group (LK- group), in which the patients received lidocaine or ketamine injection for pain control in addition to the usual intraoperative and postoperative narcotics. The allocation ratio was 1:1 (30 patients in each group).

The wide-gauge peripheral venous cannula was inserted in all patients on arrival in the induction room. Premedication with midazolam was intravenously administered at a dosage of 0.02 mg/kg. Pulse oximetry, an electrocardiogram, a heart rate (HR) monitor, noninvasive blood pressure monitoring, a gas analyzer for inspired and expired gases, and capnography were all used in the operating room for routine monitoring.

General anesthesia was intravenously induced in both groups using two µg/kg of fentanyl, 2 mg/kg of propofol, and 0.5 mg/kg of atracurium. An appropriate-size endotracheal tube was then inserted and secured. Controlled mechanical ventilation was adjusted using Aisys Carestation™ (GE Healthcare, Madison, WI, USA) to keep end-tidal CO2 between 35 and 40 mmHg. Maintenance of anesthesia was performed by 1 MAC inhalational sevoflurane in a mixture of oxygen/air with 2 L/min fresh gas flow. IV ondansetron 4 mg was administered to all patients to prevent postoperative nausea and vomiting (PONV). The intraoperative hemodynamic stability was accomplished by titrating the inhalational inspired gas concentration with intermittent IV fentanyl boluses while keeping the HR and mean arterial pressure within 20% of baseline.

In the LK group, a bolus dose of IV lidocaine (1.5 mg/kg) (17) together with IV low dose ketamine (0.25 mg/kg) (18) was administered during anesthesia induction, followed by continuous IV lidocaine infusion via a syringe pump (Injectomat Agilia®; Fresenius Kabi, Homburg, Germany) at a rate of 1.5 mg/kg/h after tracheal intubation (17). Another IV access was inserted and secured for lidocaine infusion. The infusion was maintained throughout the surgery and stopped at the termination of the surgery.

In the N group (control group), a similar volume of 0.9% saline was administered instead of lidocaine and ketamine (placebo).

Intraoperative hypotension was managed by one-unit IV colloid infusion with 5 to 25 mg slowly IV ephedrine administration. Intraoperative blood loss was carefully assessed with prompt blood transfusion whenever indicated. The intraoperative core temperature was maintained at greater than 36 °C using a warming system.

Tracheal extubation was performed at the end of the surgery after the patient regained consciousness. The remaining neuromuscular blockade was antagonized with 0.02 mg/kg neostigmine and 0.01 mg/kg atropine. All patients were then transferred to the postanesthetic care unit (PACU).

IV morphine was given as an initial 0.05 mg/kg loading dose in both groups on arrival at the PACU. The PCA morphine setting was adjusted with a bolus dose of 0.01 mg/kg, a lock-out interval of 15 minutes, and a basal infusion of 0.02 mg/kg/h (19). The infusion rates were titrated based on vital signs, numeric pain scale, and clinical status, with a maximum infusion rate of 0.06 mg/kg/h (20). PCA morphine was continued until the patient could be administered oral analgesics. Patients were trained to self-administer the analgesia by pressing the bolus knob when they experienced intolerable pain. The total opioid requirement and the numeric pain scale score (0 = no pain, 10 = worst pain) were calculated within the first 24 h after surgery and compared in the groups. Patients with a pain scale score ≥4 were administered rescue analgesia in 2 mg IV morphine. PONV was managed by IV metoclopramide (10 mg). Pruritis was managed by administering an IV antihistaminic.

The numeric rating scale (NRS) for pain was recorded upon patient arrival in the PACU and then at 2, 6, 12, and 24 hours after surgery. Postoperative sedation was evaluated using a verbal rating scale (Zero=awake, one=awake and sleepy, two=sleeping but rousable, three=sleeping but not rousable) (21). Independent investigators blinded to group allocation assessed the postoperative data. Accordingly, the study was conducted in a double-blinded manner. In the postoperative phase, all LK patients were evaluated for lidocaine toxicity symptoms (e.g., tongue paresthesia, circumoral numbness, seizures), and a lipid emulsion solution was prepared for adequate lidocaine overdose therapy. No patients showed any symptoms of toxicity.

The primary end measures were total intraoperative and postoperative opioid consumption and NRS within the first 24 hours after surgery. The secondary outcome measures were sedation score, IV

rescue analgesia, PONV, and pruritis within the first 24 hours postoperatively.

Statistical analysis

Sample size calculation: We used PASS 11.0 to calculate the sample size based on the research by Jendoubi et al. (22). A sample size of 30 patients in group I (LK group) and 30 patients in group II (N group) provided 88 % power to detect a difference of -15.6 between the null hypothesis that both groups' means were 32.0 and the alternative hypothesis that group 2's mean was 47.6 using a two-sided two-sample t-test with estimated group standard deviations of 7.0 and 5.0, and a significance level (alpha) of 0.05000.

Data analysis: We used the Statistical Package for Social Science (Armonk, NY: IBM Corp., IBM SPSS Statistics for Windows, version 23.0) for statistical analysis. The mean ± standard deviation or median (Q1, Q3) expressed quantitative variables. Frequencies and percentages were used to describe qualitative characteristics. The chi-square test was used to compare categorical (qualitative) data sets. The Kolmogorov– Smirnov test was used to investigate the distribution of data. As a result, the Student t-test was used to compare normally distributed variables in the two groups to see if there were any notable outcomes. We used the Kruskal–Wallis test first for non-normally distributed data, then the Mann–Whitney test if significant findings were detected. The confidence interval was 95%. A P value of less than 0.05 was considered significant.

Results

A total of 60 patients were evaluated for eligibility between March and October 2021. All patients agreed to participate; thus, 60 patients were randomly assigned to the two groups (n = 30 patients; Figure 1). The trial was halted when the primary outcome variables revealed highly statistically significant differences between the groups in opioid consumption in the first 24 hours and NRS score for pain.

The two groups were comparable in age, sex, weight, ASA physical status, and surgical time (P>0.05; Table 1).

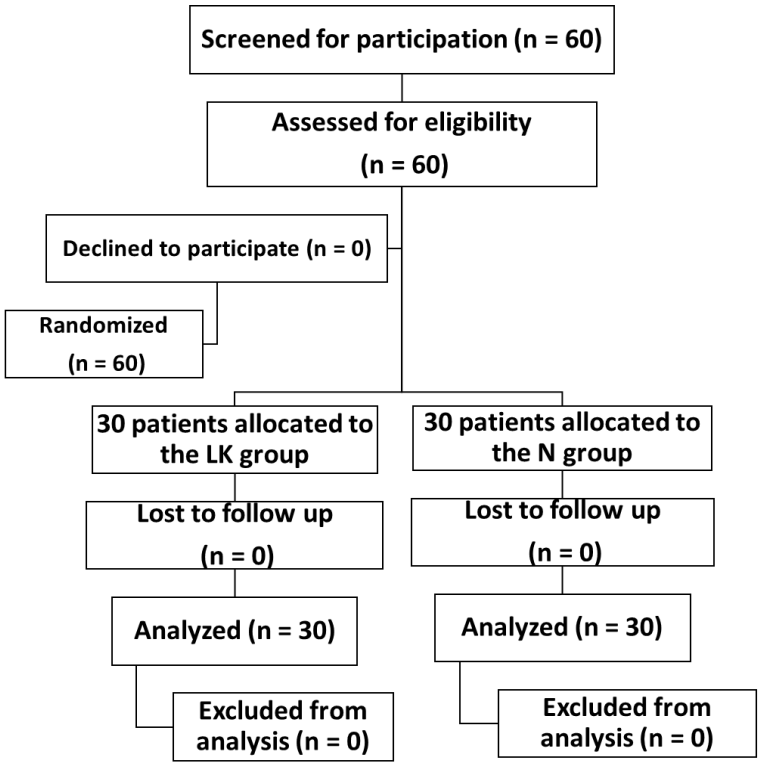

Figure 1. The trial flow chart depicts the allocation and randomization of participants.

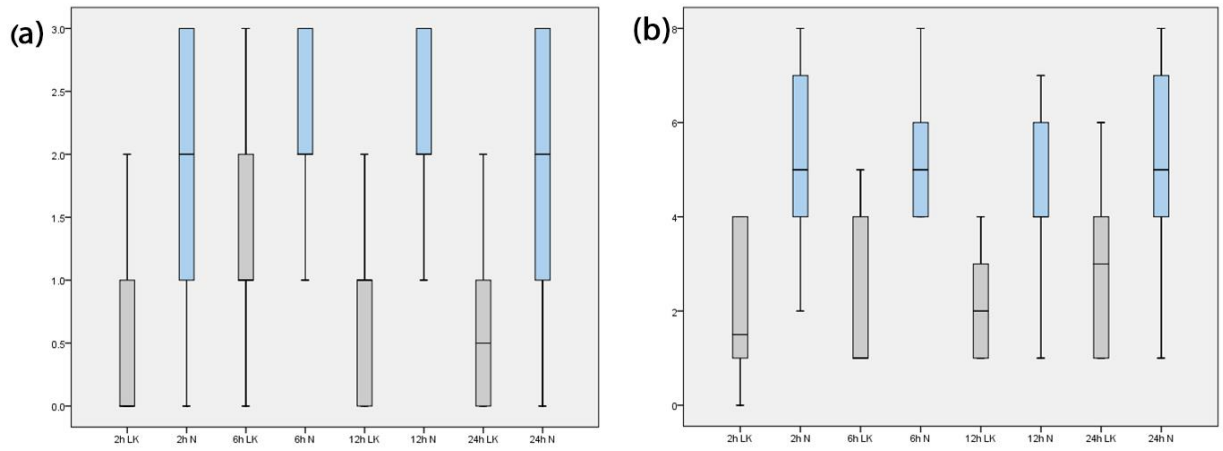

Figure 2. (a) Sedation scores in both groups during the first 24 hours following surgery (as determined by the verbal rating scale), The Q1 and Q3 percentiles are the upper and lower limits of the box, respectively. The median is the bold line that goes across the box-and-whisker plots**;** (b) Pain scores in both groups during the first 24 hours following surgery (as determined by the numeric rating scale [NRS] for pain), The Q1 and Q3 percentiles are the upper and lower limits of the box, respectively. The median is the bold line that goes across the box-and-whisker plots.

The LK group had much less intraoperative fentanyl consumption (216.3±28.8 μg) when compared with the N group (363±35 μg). In addition, the cumulative morphine consumption during the first 24 hours after surgery was significantly lower in the LK group (49.5±6.0 mg) than in the N group (57.8±8.6 mg; P<0.05; Table 2).

Patients in the LK group had a significantly lower incidence of PONV compared to that in the N group (five patients (16.7%) vs.12 patients (40%); P<0.05; Table 2).

Ten patients (33.3%) experienced postoperative pruritis in the LK group compared with 16 patients (53.3%) in the N group. The number of patients who received postoperative rescue analgesia was significantly lower in the LK group (8 patients (26.7%) as compared with 14 patients (46.7%) in the N group. (P<0.05; Table 2).

Figure 2a shows the comparison of the sedation score between the two groups. The median (Q1, Q3) sedation scores for the LK group versus the N group at 2, 6, 12, and 24 hours after surgery were 0 (0, 1) vs. 2 (1, 3), 1 (1, 2) vs. 2 (2, 3), 1 (0, 1) vs. 2 (2, 3) and 0.5 (0, 1) vs. 2 (1, 3) respectively. At all-time intervals, the differences between the two groups were statistically significant (P<0.05).

Figure 2b shows the comparison of the NRS between the two groups. The median (Q1, Q3) pain scores for the LK group versus the N group at 2, 6, 12, and 24 hours after surgery were 1.5 (1, 4) vs. 5 (4, 7), 1 (1, 4) vs. 5 (4, 6.25), 2 (1, 3) vs. 4 (4, 6) and 3 (1, 4) vs. 5 (4, 7) respectively. Patients in the LK group described lower pain scores at all-time points than those in the N group (P<0.05).

Discussion

In patients having one- or two-level posterior spine fusion surgery, we evaluated the analgesic efficacy of combined systemic lidocaine and low-dose ketamine to that of a standard narcotic-only regimen. We recruited 60 patients scheduled for spine fusion surgery and divided them randomly into two groups if they satisfied the inclusion and exclusion criteria. No patients were excluded from the study. The results demonstrated that an intraoperative systemic lidocaine infusion with a single low dose of ketamine improved postoperative analgesia with lower pain scores throughout the first 24 h, reduced intraoperative and postoperative opioid needs, and reduced opioid-related side effects.

Table 1: Demographics and surgical duration of the groups.

Variable		Group		*P*-value
		LK group	N group	
Age (y)		48.8 ± 10.5	50.1 ± 10.1	0.873
Weight (kg)		87.8 ± 11.3	84.5 ± 13.2	0.326
Sex	**Male**	17 (56.7)	14 (46.7)	0.164
	Female	13 (43.3)	16 (53.3)	
ASA	**ASA I**	14 (46.7)	7 (23.3)	0.825
	ASA II	16 (53.3)	23 (76.7)	
Duration of surgery (min)		151.3 ± 16.0	153.3 ± 21.3	0.739

Values are expressed as the mean ± SD or number of patients (%).
P > 0.05 was considered non-significant.

Table 2: Comparison of opioid consumption, postoperative complications, and the need for rescue analgesia between the groups.

Variable		LK group (n = 30)	N group (n = 30)	*P* value
Intraoperative fentanyl consumption (µg)		216.3 ± 28.8	363 ± 35.0	0.032*
24-hour morphine consumption (mg)		49.5 ± 6.0	57.8 ± 8.6	0.027*
Pruritis	**Yes**	10 (33.3)	16 (53.3)	0.039*
	No	20 (66.7)	14 (46.7)	
PONV	**Yes**	5 (16.7)	12 (40)	0.047*
	No	25 (83.3)	18 (60)	
Rescue analgesia	**Yes**	8 (26.7)	14 (46.7)	0.023*
	No	22 (73.3)	16 (53.3)	

Values are expressed as the mean ± SD or the number of patients (%).
*P < 0.05 was considered significant

Most of the previous trials studied the analgesic effects of either lidocaine infusion or ketamine

injection alone in patients undergoing spine surgeries. However, in this study, we aimed to combine the beneficial analgesic effects of both drugs in a multimodal regimen, especially with the substantial increase in the total number of spinal decompression and spine fusion procedures performed for lumbar spine degeneration.

Inadequate postoperative pain management can result in short- and long-term problems, including poor patient satisfaction, delayed patient mobilization, venous thrombosis, ischemia, and chronic pain syndromes.

Multiple authors have discussed the implication of IV lidocaine on postoperative pain management. These studies have demonstrated that IV lidocaine enhances early postoperative analgesia in various surgeries, including adult and pediatric spine surgery (23). The effects of IV lidocaine have been reported to linger for several days after infusion. This observation suggests that lidocaine reduces central and/or peripheral nervous system hypersensitivity (24). Furthermore, monoethyl-glycine-xylidide, a lidocaine metabolite, also exhibited analgesic characteristics (24). On the other hand, other trials have failed to prove that IV lidocaine has a substantial analgesic impact during the postoperative period (25).

Patients undergoing spine surgery encounter various complications, the most prevalent of which is a systemic inflammatory reaction to surgical tissue damage. Additionally, inflammatory cytokines are produced in response to glial cell activation after surgical injury, resulting in central and peripheral sensitization (23).

Kranke et al. demonstrated that perioperative lidocaine infusions more than or equivalent to 2 mg/kg/h were linked with reduced opioid intake and decreased pain scores throughout the first 24 hours (26). Another study done by Park et al. examined the analgesic effect of IV lidocaine in patients with failed back surgery syndrome. They found that 5 mg/kg of IV lidocaine was far more efficacious than 1 mg/kg in suppressing sharp and deep pain (27).

Ketamine has recently been reported to enhance mood. Because depression is expected in the postoperative period, ketamine can also ease the psychological aspect of pain (28). Multiple systematic reviews have shown that low-dose ketamine (<1 mg/kg IV bolus) can be used as an adjunct to usual opioids and local anesthesia regimens (16). Bell and colleagues observed that ketamine reduced postoperative opioid consumption (15).

Some authors believe that starting a ketamine infusion before the surgical incision, followed by intraoperative and postoperative infusions, is the best strategy to limit postoperative opioid intake. However, in our study, combining an intraoperative lidocaine infusion with low-dose ketamine administered at the induction of anesthesia resulted in a similar decrease in opioid consumption and improved postoperative pain scores.

In contrast, some authors have reported that low-dose ketamine does not reduce postoperative opioid consumption in patients undergoing PSF when given only intraoperatively. According to some research, the differences in the doses, duration, and timing of ketamine administration (29).

Our results show that the frequency of PONV in the LK group was much lower than that in the N group. This finding agrees with Vigneault et al.'s meta-analysis of the analgesic impact of IV lidocaine infusion throughout the perioperative phase. (29).

Furthermore, we found significant variances in the sedation scores between the two groups. The patients in the LK group had mild sedation and lower sedation scores during the first 24 h compared to those in the N group. This result can be explained by the fact that the consumption of opioids in the LK group was lower than that in the N group.

The limits of this study include the small sample size, the lack of measurement of the serum lidocaine level, and the follow-up period of only 24 h postoperatively. More studies are needed to compare the lidocaine alone or ketamine alone group with the two groups used in this study to demonstrate the superiority of the lidocaine/low-dose ketamine combination.

Conclusion

In patients undergoing PSF, multimodal analgesia with IV lidocaine infusion and low-dose ketamine,

when added to opioid-based analgesia, may help in reducing the postoperative pain scores and lower the opioid consumption, sedation, and opioid-related adverse effects.

Acknowledgment

None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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