Randomized Trial

Does Intraoperative Multi-Drug Wound Infiltration Relieve Postoperative Pain Following Single-Level TLIF Surgery? A Randomized Controlled Trial

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Background: How to minimize postoperative pain following spinal surgery has been a great challenge for both surgeons and patients. We hypothesized that intraoperative multi-drug wound infiltration could relieve postoperative pain following single-level transforaminal lumbar interbody fusion (TLIF) surgery.

Objectives: To evaluate the effect of intraoperative multi-drug wound infiltration for postoperative pain following single-level TLIF surgery.

Study Design: A randomized, double-blinded controlled trial (RCT).

Setting: Department of Orthopaedic Surgery, Qilu Hospital of Shandong University.

Methods: The RCT enrolled 50 patients with 25 cases in 2 groups. The study group received intraoperative wound infiltration of mixed solution with lidocaine, ropivacaine, and epinephrine before wound closure. The control group was infiltrated with an equal amount of normal saline. The primary outcome measure was the visual analog scale (VAS) of postoperative incision pain. The secondary outcome measures were the postoperative opioids dosage, the time of first analgesic demand, and the Oswestry Disability Index (ODI).

Results: The VAS of postoperative pain in the study group was significantly lower than the control group within postoperative 24 hours. The opioid dosage was significantly less and the time of first analgesic demand of patient-controlled analgesia (PCA) in the study group was significantly longer than the control group. None of the patients in the study group required analgesic supplementation. The side effects of opioids were significantly less in the study group. There was no significant difference in ODI, operation time, intraoperative blood loss, postoperative drainage, and postoperative incision complications between the 2 groups.

Limitations: Single-center study for single-level TLIF surgery.

Conclusions: Intraoperative multi-drug wound infiltration before closure could significantly relieve postoperative pain following single-level TLIF surgery.

Key words: Transforaminal lumbar interbody fusion, postoperative pain, wound infiltration, multi-drug, randomized controlled trial

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Transforaminal lumbar interbody fusion (TLIF) has been widely used around the world for the treatment of degenerative lumbar spine disorders, such as lumbar spondylolisthesis and degenerative intervertebral disc diseases (1,2). The traditional open TLIF surgery needs lamina and facet exposure with paraspinal muscle detachment, which could cause moderate or severe postoperative pain. The pain after spinal surgery has been recognized as one of the top ranks for high pain score (3), which could not be avoided absolutely.

Postoperative pain leads to a poor quality of life which makes patients feel unpleasant both mentally and physically (4). Patients with moderate or severe postoperative pain will suffer a lower level of life satisfaction, need a longer time to adapt themselves to ambulation, and be exposed to a higher risk of complications such as thromboembolic events and hospital-acquired infections (5-7). How to minimize postoperative pain is also a key point for enhanced recovery after surgery (ERAS)(8). Despite a variety of pain management strategies applied, pain relief still remains an intractable issue. Anti-inflammatory drugs (NSAIDs) and opioids are the major drugs used to manage postoperative pain. However, the side effects related to these drugs are common, such as nausea and vomiting (9).

Wound infiltration with local anesthetics has been widely reported in a variety of surgical procedures due to its safety, efficacy, simplicity, and low cost. Local anesthetic infiltration could relieve postoperative pain without gastrointestinal reactions (5). As for whether the multi-drug infiltration could relieve the postoperative pain following single-level TLIF surgery, the current RCT was conducted to comprehensively evaluate the analgesic effect of multi-drug with lidocaine, ropivacaine, and epinephrine.

Methods

The double-blind, randomized controlled trial was performed in line with the principles of the Declaration of Helsinki and was approved by the ethics committee of the local Hospital. The clinical trial number of this study was ChiCTR2200056420. Written informed consent was obtained from all patients before enrollment. The research was conducted between January 2022 and March 2022. The patients with lumbar degenerative diseases (including spondylolisthesis, lumbar instability, lumbar spinal stenosis, etc.) who received single-level TLIF surgery were included. The exclusion criteria included a history of lumbar surgery, history of chronic pain with long-term opioid therapy, allergic or intolerant to the interventional drugs, accompanied by severe liver, kidney, and cardiovascular diseases, and refusing to participate.

All patients were instructed on how to assess incision pain by using the visual analog scale (VAS) ranging from 0 (no pain) to 10 (worst pain) and using a patient-controlled analgesia (PCA) device before surgery. All the surgical and anesthesia procedures were performed by the same surgeons and anesthetists teams.

Sample Size

According to the literature review and the results of the pre-experiment, the average VAS score of the study group was 3.4, and that of the control group was 5.2, with a standard deviation of 1.62. Power Analysis and Sample Size (PASS 15, NCSS, LLC. Kaysville, Utah) software was used to calculate the sample size. With a type I error (α) of 5% and a power (1-β) of 90%, a sample size of 19 patients in each group would be required. If a 20% dropout rate was taken into account, a total of 24 cases were needed for each group. Based on this, at least 48 cases were needed, and we planned to recruit about 50 cases in the study.

Study Procedure

Fifty patients were recruited eventually. Each individual was randomly allocated to the study group or control group. The study group (n = 25) received infiltration of multi-drug before wound closure of surgery. The control group (n = 25) was infiltrated with the same amount of normal saline. All patients in both groups received PCA postoperatively with an analgesia pump filled with the same drugs. There was no patient lost during the postoperative 1-month follow-up. The flow diagram of the study is shown in Fig. 1.

The open TLIF surgery was performed by the same surgeon's team. After the exposure, decompression, discectomy, interbody fusion, and internal fixation were performed step by step. The general anesthesia procedure was performed by the same anesthetist's team with the same protocol. Each individual was premedicated with midazolam 0.03 mg/kg IV 3 minutes before induction and followed a standardized general anesthesia protocol (etomidate 0.2-0.3mg/kg, sufentanil 0.3-0.5ug/kg, and rocuronium 0.6-0.8mg/kg). After surgery, each subject had access to IV PCA with analgesia pump (sufentanil citrate 100 μg) for 48 hours

(1-μg demand bolus, 15-min lockout, limit 10 μg/4 h).

The mixed drugs used in the current study included lidocaine, ropivacaine, and epinephrine. The mixed solution was prepared by adding lidocaine 400 mg (20 mL), ropivacaine 100 mg (5 mL), epinephrine (1:1000) 0.25 mg (0.25 mL) mixed with normal saline solution 24.75 mL. The total volume of the multi-drug solution was 50 mL, which was infiltrated into paraspinal muscles bilaterally and subcutaneous tissue under the incision (Fig. 2).

Randomization was achieved by the sealed envelope method: pieces of paper with group names written on them were placed in sealed envelopes. An independent secretary not involved in this study pulled out an envelope for each patient and prepared the solutions for the study and control groups. Patients, surgeons, and postoperative pain evaluators were all blinded.

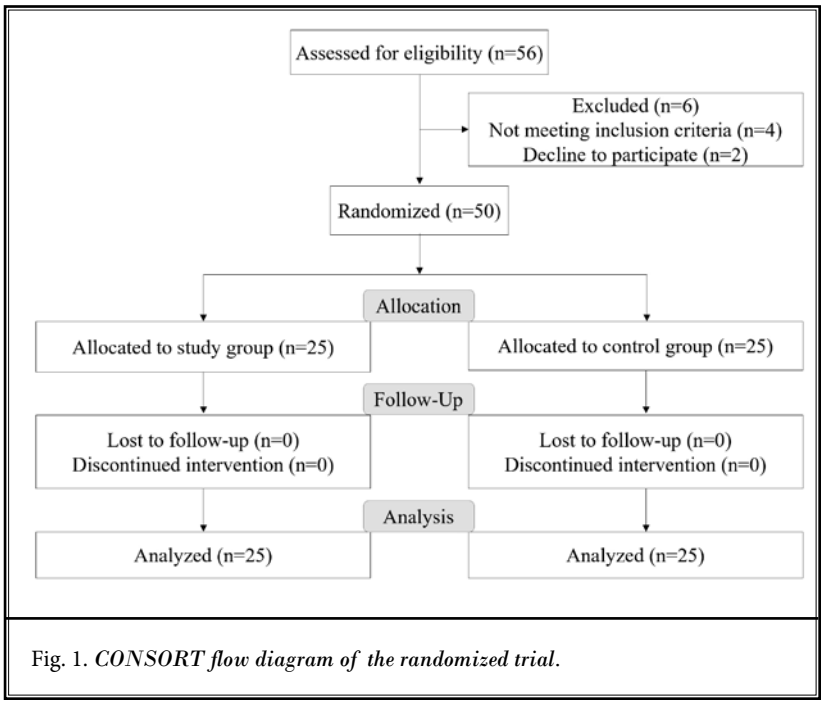

Fig. 1. *CONSORT flow diagram of the randomized trial.*

Fig. 2. *Multi-drug was infiltrated into paraspinal muscles bilaterally and subcutaneous tissue under the incision before closure.*

Outcome Assessment

The time of the first analgesic demand of PCA was recorded. Sufentanil consumption was measured at first 12 hours, between 12-24 hours, and 24-48 hours, and the cumulative dose was calculated. After recovery from anesthesia, all patients were asked to indicate the resting VAS scores at 6-hour intervals for the 48 hours postoperatively. For cases with a VAS score > 5, the application of 50 mg IV flurbiprofen axetil was planned as a rescue analgesic. The times and total amount of flurbiprofen axetil administration were recorded. The side effects were recorded, including postoperative nausea or vomiting, and intramuscular injections of 10 mg metoclopramide was used for symptomatic treatment. In addition, Oswestry Disability Index (ODI) (preoperatively and at postoperative 1-month follow-up), operation time, intraoperative blood loss, postoperative drainage, and postoperative incision complications (infection or poor healing) were recorded.

Statistical Analysis

Means and standard deviations were calculated for continuous variables. Differences between the 2 groups, preoperative and postoperative parameters, were determined by the independent sample t test. The chi-square test was performed to analyze the categorical variables. $P < 0.05$ was considered statistically significant. Statistical measures were performed using Statistical Package for Social Science version 25.0 (IBM Corporation, Armonk, NY).

Results

Patients Population

A total of 50 patients (25 patients in the study group, and 25 patients in the control group) were analyzed in the current study. The patients' characteristics are summarized in Table 1. There were no significant differences in age, gender, BMI, and surgical level between the 2 groups.

Outcomes Analysis

The resting VAS scores of postoperative low back pain reported by patients were significantly lower in the study group than those in the control group at all assessment times (6 hours, 12 hours, 18 hours, 24 hours, 30 hours, 36 hours, 42 hours, and 48 hours after surgery) ($P < 0.05$) (Fig. 3). Fourteen patients (56%) in the study group did not need postoperative PCA analgesia. There was statistically significant less sufentanil consumption in the study group than the control group during the first 12 hours, 12-24 hours, and 24-48 hours after surgery ($P < 0.05$). The cumulative dose of sufentanil consumption in the study group was significantly lower than that in the control group ($P < 0.05$) (Table 2).

The time of the first analgesic demand of PCA in the study group was significantly longer than that in the control group ($P < 0.05$). None of the patients in the study group required postoperative analgesic supplementation. But in the control group, 11 (44%) patients received 50 mg flurbiprofen axetil for analgesia within 48 hours after surgery, of which 2 (8%) patients consumed 100 mg flurbiprofen axetil. The side effects of opioids were significantly less in the study group than that in the control group ($P < 0.05$). There was no significant difference in ODI, operation time, postoperative drainage, and postoperative incision complications between the 2 groups ($P > 0.05$).

Table 1. *Demographic of the patients.*

	Study (n = 25)	Control (n = 25)	*P* Value
Gender (male/female)	11/14	13/12	0.571
Age (yr)	58.32 ± 8.78	57.80 ± 8.83	0.835
Body Mass Index (kg/m^2)	26.07 ± 3.53	25.44 ± 4.25	0.573
Surgical level (n)			
L4-5	19	21	0.480
L5-S1	6	4	0.480
Operation time (min)	149.20 ± 10.28	145.60 ± 11.67	0.253
Intraoperative blood loss (mL)	177.20 ± 24.92	174.80 ± 21.24	0.716

Data are given as (n) or mean ± SD; $P < 0.05$ was considered significant

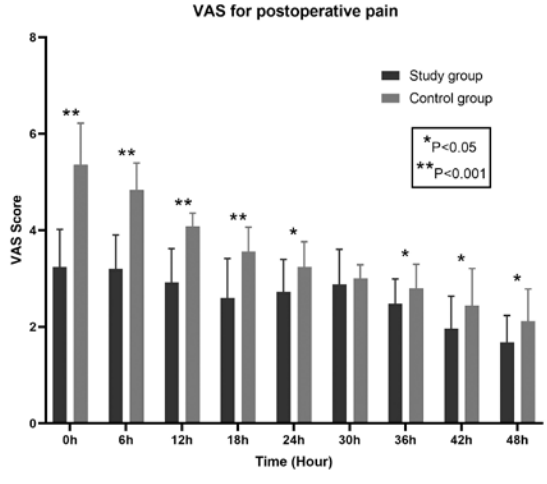

Fig. 3. *The assessment of VAS for postoperative pain.*

Discussion

TLIF surgery has been widely used around the world, and the postoperative pain has always been a challenge for both surgeons and patients (3) due to the extensive dissection of paraspinal muscle (10). Acute unrelieved postoperative pain could also stimulate the autonomic nervous system releasing the catechol-

Table 2. *Postoperative outcome analysis.*

	Study (n = 25)	Control (n = 25)	*P* Value
Sufentanil usage (μg)			
0-12 h	0.52 ± 0.77	4.52 ± 1.61	0.000
12-24 h	0.20 ± 0.41	2.32 ± 0.75	0.000
24-48 h	0.08 ± 0.28	0.72 ± 0.54	0.000
Cumulative dose	0.80 ± 1.12	7.56 ± 2.55	0.000
First analgesic demand (min)	287.27.00 ± 430.21	52.20 ± 47.08	0.010
Postoperative drainage (mL)	95.60 ± 23.11	105.20 ± 21.04	0.131
Side effects (n)	2	13	0.001
Nausea	2	11	
Vomiting	0	2	
Incision complication (n)	0	0	—
Infection	0	0	
Poor healing	0	0	
Oswestry Disability Index			
Preoperative	63.52 ± 8.29	64.12 ± 8.43	0.801
1-month follow-up	24.88 ± 3.33	25.28 ± 2.92	0.654

Data are given as (n) or mean ± SD; $P < 0.05$ was considered significant

amines and leading to postoperative cognitive dysfunction (11). In addition, postoperative pain itself is a risk factor for the development of chronic persistent pain in 10% to 50% of individuals after operations (12). Optimizing postoperative pain control is a critical aspect of the ERAS that enables earlier ambulation, reducing time in bed and complications and decreases the length of hospital stay (5,13).

Nowadays, the general analgesic regimen for postoperative pain, including spine surgery, has become the administration of intra- and post-operative NSAIDs or opioids. PCA has also been widely used to relieve postoperative pain, especially after spine surgery (14). Despite the significant analgesic effect of opioid administration, the related side effects of opioids occur with high incidence and cannot be avoided, including nausea and vomiting, especially for aged patients. Hence, how to relieve the postoperative pain has been the focus of both clinical surgeons and patients. A variety of clinical studies have been conducted to evaluate and explore a better regimen for postoperative pain management.

Wound infiltration with local anesthetics for postoperative pain relief could be an attractive method, which can theoretically improve early postoperative pain control and minimize the demand for opioids, thereby reducing the well-known adverse reactions of opioids (5). In fact, Mullen et al (15) first recommended local anesthetic penetration after spinal surgery in a technical report in 1979. Since then, lots of studies have been conducted to analyze and explore excellent local analgesic regimes, and local anesthetic wound infiltration has been widely used in spinal surgery. Previous studies have proved the positive effect of local anesthetics on pain control after spinal surgery (16-18).

As for the regime of local anesthetic infiltration, despite a single drug could also effectively relieves postoperative pain (19,20), multi-drug infiltration has been proven to be more effective. Ozyilmaz et al (21) found that the combination of levobupivacaine and tramadol had a significantly better analgesic effect on wound infiltration than levobupivacaine or tramadol alone. Abdel Hay et al (22) reported that wound infiltration with combined bupivacaine and clonidine could better control postoperative pain after spinal surgery and reduce the dosage of opioids compared with bupivacaine alone. Multi-drugs for local infiltration include NSAIDs, opioids, local anesthetics, and epinephrine, which may act through different mechanisms and enhance the synergistic effect (23).

In the current study, the mixed local anesthetic drugs of lidocaine, ropivacaine, and epinephrine were used. As one of the most commonly used local anesthetics, lidocaine has been widely used in various surgical procedures and could relieve postoperative pain, decrease opioid demand, and accelerates convalescence (24). With the characteristics of longer effecting time and less cardiotoxicity risk, wound infiltration of ropivacaine could significantly reduce postoperative pain, mitigate supplemental analgesic demand after TLIF (25). Local infiltration of epinephrine could promote vasoconstriction in the tissue, reduce intraoperative bleeding, delay the absorption of local anesthetics and prolong the anesthetic effect (26). In the meantime, previous research has proven that local anesthetics have antimicrobial effect potential in addition to their anesthetic and analgesic effects, especially when used in combination with adrenaline, which could positively contribute to wound healing by preventing and treating wound infections (27).

In order to evaluate the clinical effect of drug infiltration objectively, the randomized controlled trial was performed with double-blinded patients, surgeons, and outcome evaluators. The operation and general anesthesia were performed by the same surgeons and anesthetists teams, with the aim to minimize the effect of confounding factors. Compared with the control group, the VAS score of postoperative pain in the study group was significantly lower, the time of first analgesic demand of PCA was significantly longer, and the consumption of opioids decreased significantly during 48 hours postoperative. In addition, 56% of patients in the study group did not need postoperative PCA for analgesia. None of the patients in the study group required postoperative analgesic supplementation. But in the control group, 44% of patients needed additional anesthetics. The side effects of opioids in the study group were relatively small, mainly because of the less dosage of opioids.

In addition, the postoperative drainage in the study group was less, but there was no significant difference compared with the control group. However, Kraiwattanapong et al (6) found that the postoperative drainage of split lumbar laminectomy in the multimodal drugs infiltration group trended to increase more than the control group, which may be because of the increased activity after pain relief. The reason for less drainage in the current study group may be the effect of reducing bleeding of epinephrine in the surgical wound (28,29). There was also no significant difference in ODI during

the follow-up between the 2 groups. As for the incision complication, all the patients in both groups achieved excellent healing without infection.

Limitations

There were some limitations to the current study. Firstly, all the patients included in the study underwent only single-level traditional open TLIF surgery. As for the analgesic effect following multi-level surgery, further studies are needed. Secondly, the primary observational measurement was the VAS score for postoperative pain, which was a subjective grading method and may result in some bias due to different pain thresholds for different people. Thirdly, the current study is a single-center RCT with the same surgeons and anesthetists teams with a small sample size. Further multi-center RCTs with a large sample are needed.

Conclusions

Intraoperative multi-drug wound infiltration before closure could significantly decrease postoperative pain following single-level TLIF surgery. It could reduce postoperative opioid requirements and prolong the time of first analgesic demand with no increased side effects. Intraoperative multi-drug wound infiltration is a simple, safe, effective ,and low-cost method and a good choice for postoperative pain management. Furthermore, multi-center RCTs are needed to comprehensively evaluate the procedure of local analgesic wound infiltration.

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