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Randomized Controlled Trial

Effect of Topical Nonsteroidal Anti-inflammatory Drugs Around the Incision on Postoperative Pain in Transforaminal Lumbar Interbody Fusion Surgery: A Double-blind Randomized Controlled Trial

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Background: How to minimize postoperative pain following spinal surgery has been a great challenge. We hypothesized that topical nonsteroidal anti-inflammatory drugs (NSAIDs) around the incision could relieve postoperative pain following transforaminal lumbar interbody fusion (TLIF) surgery.

Objective: This study tested the effect of topical NSAIDs around the incision for pain management after TLIF surgery.

Study Design: A double-blind randomized controlled trial.

Setting: Qilu Hospital of Shandong University.

Methods: Eighty patients who underwent single-level TLIF surgery were randomized into 2 groups. The treatment group received postoperative topical NSAIDs around the incision. The control group received a postoperative topical placebo around the incision. All patients in both groups received postoperative patient-controlled analgesia (PCA) via an analgesia pump. The primary outcome measures were the amount of opioid consumption and pain measurement via the visual analog scale (VAS). The secondary outcome measures were the time of first analgesic demand, operation time, postoperative drain output, side effects of opioids, postoperative stay, and Oswestry Disability Index (ODI) score.

Results: The consumption of opioids in the treatment group was significantly less than in the control group at postoperative 12 hours, 12 to 24 hours, and 24 to 48 hours ($P < 0.005$). The VAS in the treatment group was significantly lower than those in the control group at all assessment times within 72 hours postoperative ($P < 0.005$). The time of first analgesic demand of PCA in the treatment group was significantly longer than that in the control group ($P < 0.005$). The side effects of opioids were significantly less in the treatment group than in the control group ($P < 0.05$). There was no significant difference in operation time, postoperative drain output, postoperative stay, and ODI between the 2 groups ($P > 0.05$).

Limitations: This was a single-center study for single-level TLIF surgery.

Conclusion: Postoperative topical NSAID around the incision is a highly effective and safe method for postoperative pain management following single-level TLIF surgery. In our study it reduced postoperative opioid requirements and prolonged the time of first analgesic demand with no increased side effects.

Key words: Transforaminal lumbar interbody fusion, postoperative pain, NSAID, topical NSAID, nonsteroidal anti-inflammatory drug, loxoprofen

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Postoperative pain is the unpleasant emotional and sensation experience that leads to a poor quality of life for many patients worldwide (1,2). High levels of postoperative pain are associated with decreased patient satisfaction and delayed postoperative ambulation, increasing complication risks, such as thromboembolic events and hospital-acquired infections (3-5).

Degenerative lumbar disorders are most prevalent in the elderly and decrease their mobility and quality of life (6). Its prevalence continues to rise due to the aging population (7,8). In the case of clinical deterioration or failed conservative management, surgery should be considered. Transforaminal lumbar interbody fusion (TLIF) is a safe and effective method for the treatment of degenerative lumbar spine disorders (9,10). But TLIF surgery requires lamina and facet exposure with paraspinal muscle detachment, which could cause moderate or severe postoperative pain.

Pain after spinal surgery ranks high among procedures for a high pain score; pain management is usually inadequate (11). Despite a variety of pain management strategies, patients undergoing spinal surgery still suffer in the immediate postoperative period (12-14).

Enhanced recovery after surgery (ERAS) has attracted widespread attention in recent years (15,16). The important part of ERAS is adequate analgesia (16,17). Opioids have traditionally been administered to control postoperative pain. But common complications, such as nausea and vomiting, have led researchers to look for better ways to manage surgical pain (18).

A previous study (19) reported that topical nonsteroidal anti-inflammatory drugs (NSAIDs) offer similar efficacy to the oral route for relief with an improved safety profile due to their reduced systemic absorption. This makes it a very attractive option because of its safety and simplicity. However, the research on the postoperative application of topical NSAIDs in lumbar surgery is limited. Therefore, our randomized controlled trial (RCT) was carried out to assess the effect of topical NSAID around the incision on postoperative pain relief and opioid consumption following single-level TLIF surgery.

Methods

Our RCT was performed and approved by the ethics committee of Qilu Hospital of Shandong University (KYLL-202209-005-1). Informed consent was obtained from all patients before enrollment. The clinical trial number of this study is ChiCTR2200065402. This research was conducted from October 2022 through February 2023. The inclusion criteria were as follows: patients with a lumbar degenerative disease with surgical indications (including spondylolisthesis, lumbar instability, lumbar spinal stenosis, etc.); a single segmental fusion of the lumbar spine. The exclusion criteria were a history of lumbar surgery; a history of opioids to control pain; patients needing multisegmental fusion surgery; patients allergic or intolerant to the interventional drugs used; patients with severe liver, kidney, and cardiovascular disease; and patients refusing to participate.

All patients were instructed how to assess pain using the Visual Analog Scale (VAS) ranging from 0 (no pain) to 10 (worst pain) and the use of the patient-controlled analgesia (PCA) device. All the surgical and anesthesia procedures were performed by the same surgical team and anesthesia team.

Sample Size

Our study was an RCT. The postoperative 12 hour opioid consumption was used as the outcome measure. According to the literature review and the results of the pre-experiment, the mean postoperative 12 hour opioid consumption of the treatment group was 5.3, and that of the control group was 6.7, with a standard deviation (SD) of 1.7. Power Analysis and Sample Size (PASS) software, version 15 (NCSS Statistical 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 32 patients in each group would be required. If a 20% dropout rate was taken into account, a total of 40 patients were needed for each group. Based on this, we planned to recruit a total of at least 80 patients.

Study Procedure

Eighty patients were recruited. Each patient was randomly allocated to either the treatment group or the control group. The treatment group (n = 40) received postoperative topical NSAIDs around the incision. The control group (n = 40) received a postoperative placebo around the incision. All patients in both groups received postoperative PCA with an analgesia pump filled with the same drugs. The flow diagram of the study is shown in Fig. 1.

The topical NSAID we administered for postoperative pain control was loxoprofen sodium cataplasm (LSC) (Hunan Jiudian Pharmaceutical Co., Ltd.), which contained 100 mg active loxoprofen sodium per unit. The placebo contained the same ingredients as LSC apart from the loxoprofen sodium and had physi-

cal characteristics similar to LSC. The LSC was administered around the incision in the immediate postoperative period, and at 24 hours and 48 hours postoperatively in the treatment group, while the placebo was used in the control group. After using LSC or placebo, all incisions were covered with sterile gauze.

Each individual was premedicated intravenously with midazolam 0.03 mg/kg 3 minutes before induction. We followed a standardized general anesthesia protocol (etomidate 0.2-0.3 mg/kg, sufentanil 0.3-0.5 ug/kg, and rocuronium 0.6-0.8 mg/kg). After surgery, each subject had access to intravenous PCA with an analgesia pump (sufentanil citrate 100 μg) for 48 hours (1-μg demand bolus, 15-minute lockout, limit 10 μg/4h).

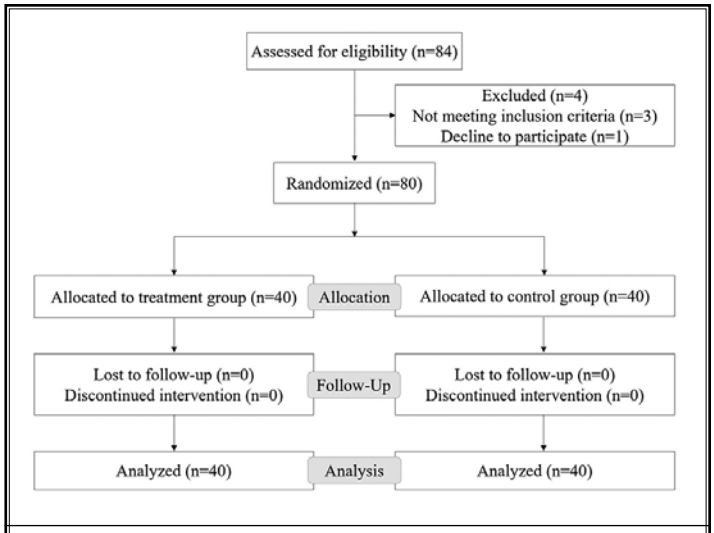

Fig. 1. *CONSORT flow diagram of the randomized trial.*

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 study solutions for the treatment and control groups. Patients, surgeons, and postoperative pain evaluators were all blinded.

Outcome Assessment

The primary outcome measures were sufentanil citrate consumption and VAS scores for back pain. Sufentanil citrate consumption was measured at the first 12 hours, between 12-24 hours, 24-48 hours, and cumulative dose. After recovery from anesthesia, each patient was asked to indicate the resting VAS scores at 8 hours, 16 hours, 24 hours, 36 hours, 48 hours, and 72 hours postoperatively. The time of first PCA analgesic demand was recorded. For patients with a VAS score ≥ 6, administration of intravenous 50 mg flurbiprofen axetil was the rescue analgesic. The flurbiprofen axetil administration times and total amounts of flurbiprofen axetil administered were recorded. Patients who developed side effects (postoperative nausea or vomiting) were recorded; they received intramuscular injections of 10 mg metoclopramide. In addition, operation time, postoperative drain output, opioid side effects, postoperative stay, and Oswestry Disability Index (ODI) score (preoperatively and at one-month follow-up) were recorded.

Statistical Analysis

Means and standard deviations were calculated for continuous variables. The data satisfying normal distribution between the 2 groups, preoperative and postoperative parameters were determined by the independent-sample t test. The χ^2 test was performed to analyze the categorical variables. $P < 0.05$ was considered statistically significant. Statistical measures were performed using IBM SPSS Statistics 25.0 (IBM Corporation).

Results

Patient Population

A total of 80 patients (40 patients in the treatment group, 40 patients in the control group) were analyzed. The patients' characteristics are summarized in Table 1. There were no significant differences in age, gender, and body mass index between the 2 groups.

Clinical Outcomes

There was statistically significant less sufentanil consumption in the treatment group than in the control group during the first postoperative 12 hours, 12-24 hours, and 24-48 hours ($P < 0.005$). The cumulative dose of sufentanil consumption in the treatment group was significantly lower than that in the control group ($P < 0.005$). The resting VAS scores of postoperative low back pain reported by the patients were significantly lower in the treatment group than those in the control group at all assessment times (postoperative 8, 16, 24, 36, 48 and 72 hours) ($P < 0.005$) (Fig. 2).

The time of the first PCA demand in the treatment group was significantly longer than that in the control group ($P < 0.005$). Two patients (5.0%) in the treatment

group received 50 mg flurbiprofen axetil for analgesia within 72 hours postoperative, while 9 (22.5%) patients in the control group consumed 50 mg flurbiprofen axetil in the same time period. The incidence of opioid side effects was significantly lower in the treatment group than in the control group (10.0% vs 27.5%, $P < 0.05$). There was no significant difference in operation time, postoperative drain output, postoperative stay, and ODI between the 2 groups ($P > 0.05$) (Table 2).

Discussion

Spinal surgeries are ranked as one of the top procedures causing the highest degree of postoperative pain (11). Managing postoperative pain following lumbar surgery is challenging due to the extensive dissection of subcutaneous tissues, bones, and ligaments during these procedures. This postoperative pain is severe and typically lasts for 3 days (20). Acute unrelieved postoperative pain also stimulates the autonomic nervous system, resulting in the release of catecholamines and postoperative cognitive dysfunction (21). Optimizing postoperative pain control is a critical component of the postoperative recovery process. It enables increased patient satisfaction, earlier ambulation, a reduced length of stay, and prevents complications associated with decreased mobility (3,22).

The administration of intra- and postoperative NSAIDs or opioids can effectively relieve postoperative pain, including pain from spine surgery. Additionally, PCA has also been widely used to control postoperative pain, especially in spine surgery (23). Intravenous opioid administration for postoperative pain is useful, but may require high opioid doses. This can increase side effects and the risks of long-term usage and dependence (24,25). Opioid side effects, including nausea and vomiting, occur with a high incidence and often cannot be avoided, especially for elderly patients. Therefore, how to relieve postoperative pain and reduce postoperative opioid use has been a focus for surgeons and patients. A variety of clinical studies have been conducted to evaluate and explore a better regimen for postoperative pain management.

Previous studies have found that administering opioids topically at the surgical site can tap its advantages (3,21,26). Although topical opioids generally

Table 1. *Patient demographics.*

	Treatment group	Control group	*P* Value
Number of patients	40	40	-
Gender (men/women)	17/23	15/25	0.648
Age (yr)	59.73 ± 9.46	59.48 ± 10.85	0.913
Body Mass Index (kg/m^2)	24.87 ± 3.98	25.22 ± 3.13	0.663
Spinal level (n) L4-L5 L5-S1	 27 13	 29 11	0.626 - -

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

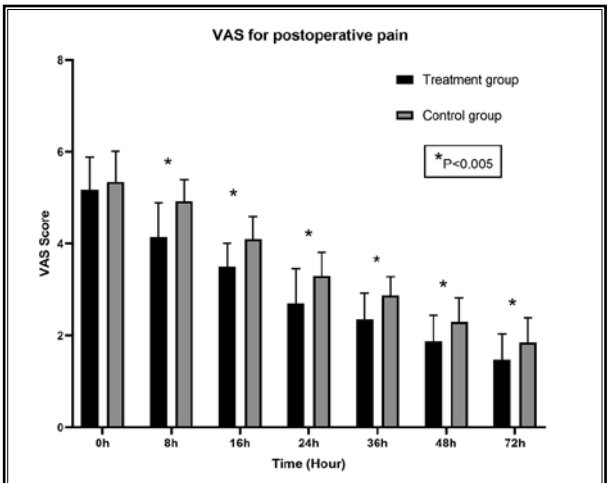

Fig. 2. *The VAS scores (mean and standard deviation) in the treatment group and the control group at different time intervals in the postoperative period.*

Table 2. *Postoperative clinical outcomes.*

	Treatment group	Control group	*P* Value
First analgesic demand (min)	110.75 ± 51.51	70.75 ± 44.17	0.000
Sufentanil citrate usage (μg) 0-12 hours 12-24 hours 24-48 hours Cumulative dose	 5.23 ±1.12 3.50 ± 1.10 1.48 ± 0.98 10.20 ± 2.45	 6.88 ± 1.78 4.63 ± 1.64 2.42 ± 1.19 13.93 ± 3.51	 0.000 0.000 0.000 0.000
Side effects of opioids (n) Nausea Vomiting	4 3 1	11 9 2	0.045
Operation time (min)	133.25 ± 10.41	130.63 ± 12.04	0.300
Postoperative drain output (mL)	104.75 ± 20.87	98.75 ± 25.83	0.257
Postoperative stay (d)	4.05 ± 0.78	4.20 ± 0.85	0.415
Oswestry Disability Index Preoperative One-month follow-up	 62.30 ± 8.17 24.70 ± 3.28	 62.93 ± 8.24 24.93 ± 3.15	 0.734 0.756

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

retain all the important analgesic effects of opioids, they are obviously devoid of the systemic side effects of opioids, such as respiratory depression and nausea and vomiting. Hence, many studies on the topical use of opioids have been conducted for improving pain control after spinal surgery with different drugs and different ways of administration.

A previous study (27) reported a double-blind randomized controlled trial of intrathecal injection of one mg of morphine after lumbar surgery. The average postoperative pain score was significantly decreased in the intrathecal morphine group, but in this same group the incidence of pruritus was higher (27). Some studies have evaluated the local instillation of epidural morphine and other drugs as a cocktail for postoperative pain control after spinal surgeries (13,21). They reported epidural PCA provided superior analgesia and higher patient satisfaction. However, Schenk et al (13) found that 18% of the patients developed transient motor block on the day of operation. In addition, some authors have highlighted the risk of respiratory depression and other side effects, which restricts the common usage of epidural opioid administration (28,29).

Rannou et al (19) reported that topical NSAIDs offer similar efficacy to the oral route for relief and have an improved safety profile due to their reduced systemic absorption. Topical NSAIDs for postoperative pain relief could be an attractive method. It can theoretically improve early postoperative pain control and minimize the demand for opioids, thereby reducing the well-known adverse reactions of opioids (30).

At present, there are many commonly used topical preparations. Loxoprofen is a widely prescribed prodrug of phenyl mefenamic acid, a nonselective NSAID associated with fewer NSAID-related adverse events (31). Loxoprofen sodium cataplasms, a kind of transdermal delivery preparation based on hydrophilic polymer materials, penetrates directly into the affected site through the topical route, resulting in consistent and safe pain relief. Therefore, we selected loxoprofen sodium cataplasms as the topical NSAID and evaluated its effect on incision pain relief and opioid consumption post-TLIF surgery.

In order to evaluate the clinical effect of this topical NSAID objectively, our RCT was performed by double-blinding the surgeons, patients, and outcome evaluators. In order to minimize the effect of confounding factors, the general anesthesia and operation were performed by the same anesthesiologist's and surgeon's team. Compared with the control group, the consumption of opioids in the treatment group decreased significantly during at 48 hours postoperative, the VAS score of postoperative pain was significantly lower, and the time of first analgesic demand of PCA was significantly longer. In addition, 2 patients (5.0%) in the treatment group received 50 mg flurbiprofen axetil for analgesia within 72 hours postoperative, but 9 (22.5%) patients received 50 mg flurbiprofen axetil in the control group. The side effects of opioids in the treatment group were relatively small, mainly due to the smaller opioid dosage.

The average value of postoperative drainage in the treatment group was more than that of the control group, but there was no significant difference. We concluded that the postoperative pain in the treatment group was significantly reduced, so there were more activities on postoperative day one or the day after, which may have led to an increase in postoperative drainage. There was no difference in the postoperative stay between the treatment and control groups, because most of the patients in the 2 groups were discharged after removal of the drainage tube. In addition, there was also no significant difference in the ODI score at follow-up between the 2 groups. As for the incision complication, all the patients in both groups achieved excellent healing without any infection.

Limitations

There are some limitations in this study. The patients in this study underwent only single-level TLIF surgery. The pain after multisegmental TLIF may be more severe, so a further RCT should be performed in multisegmental spinal fusion surgery in the future. In addition, this study is a single-center RCT with a small sample size, so further multicenter RCTs with a large sample are needed.

Conclusion

Postoperative topical NSAID around the incision is a highly effective and safe method for postoperative pain management following single-level TLIF surgery. It could reduce postoperative opioid requirements and prolong the time of first analgesic demand with no increased side effects. Furthermore, multicenter randomized controlled trials are needed to comprehensively evaluate the administration of a topical NSAID for postoperative pain.

Authors' Contributions

Chao Li, Hui Wang, and Suomao Yuan carried out the entire procedure including the study design, data

extraction, statistical analysis, manuscript writing, and editing. Xinyu Liu and Lianlei Wang conceived of the study and coordinated and participated in the entire process of drafting and editing the manuscript. Hui Wang contributed to the data extraction-literature review, and statistical analysis. Suomao Yuan and Yonghao Tian contributed to the study design and data analysis. All authors contributed significantly. All authors read and approved the final manuscript.

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