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ORIGINAL INVESTIGATION

Effect of continuous intra-incisional bupivacaine on postoperative pain in non-traumatic spinal fixation surgeries: a randomized controlled trial

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Abstract
Background: Continuous injection of local anesthetics by using surgical wound catheters for postoperative pain relief has gained acceptance in recent years. However, whether this method can be alternatively used instead of systemic opioids in different surgical procedures has not yet been elucidated.
Objectives: The aim was to investigate the effect of continuous injection of bupivacaine through a catheter inside the surgical wound on reducing the postoperative pain of lumbar spine fusion surgeries.
Methods: In this clinical trial, 31 patients undergoing non-traumatic lumbar spine stabilization surgery were randomly assigned to receive (n = 15) or do not receive (n = 16) bupivacaine through a catheter inside the surgical wound, postoperatively. Pain intensity (NRS), dose of required morphine, and drug-related complications within 24 hours of intervention were assessed and compared by the Mann-Whitney and independent *t*-test.
Results: Mean pain intensity was significantly lower in the case group over the first postoperative hour in the recovery room ($p < 0.001$), which continued for the first 2 hours after entering the ward. The mean morphine intake was lower in the bupivacaine group during the first postoperative 24 hours (16 ± 0.88 vs. 7.33 ± 0.93 mg, $p < 0.001$). The two groups were not significantly different regarding drug-related complications.
Conclusion: Continuous intra-incisional infusion of bupivacaine helped better pain reduction during the early postoperative hours while sparing morphine consumption in the first postoperative day.

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Introduction

Spinal fusion is a painful procedure whose postoperative pain relief has always been a challenging issue. Implementing the appropriate pain reduction protocol not only improves the outcome, but also decreases the pain and likelihood of postoperative morbidity, as well as hospitalization and healthcare costs.[1,2] The systemic inflammatory response causes surgical tissue damage, which is a common mechanism for adverse effects in patients with spinal fusion surgery.[3] Chronic and neuropathic pains are caused by peripheral and central sensitization, which is triggered by nitric oxide, free radicals, and excitable amino acids induced by activated glial cells and the production of cytokines in surgical wounds. The challenge of postoperative pain relief in these patients is most commonly managed via painkillers.[4]

Bupivacaine, an amide local anesthetic with unique properties, is used in regional, epidural, and spinal anesthesia, as well as local infiltration.[5] Local anesthesia commonly increases the threshold for electrical stimulation and consequently blocks the action potential in nerve cells.[6] Local anesthetics have long been administered through local tissue infiltration for pain relief.[7] Topical tissue infiltration with bupivacaine is reported as an efficient pain reliever after lumbar discectomy.[8] Bupivacaine with a half-life of 2.7 hours, being an intermediate-acting local anesthetic, reduces the pain more effectively in continuous infusion.[9] Catheters can be inserted into surgical wounds for topical and continuous injection of bupivacaine.[10]

Neuropathic pain is a common complication following spinal cord injuries and spinal surgeries.[11] Like most traditional treatment protocols, opioids are generally prescribed to reduce pain after spinal surgeries.[12] Morphine sulfate is a classic analgesic opioid that helps manage pain intensity by decreasing the activation of autonomic nervous system. Over the past decade, opioids have been increasingly used after spine stabilization surgery during admission and after discharge.[13] However, concerns exist about the risk of patient long-term dependency on opioid compounds after spine surgeries.[14,15] As already addressed in the literature, alternative methods can prevent such harmful effects.[16]

This study aimed to investigate the effect of continuous injection of bupivacaine via an intra-incisional catheter on reducing the postoperative pain of lumbar spine stabilization surgeries.

Methods

This randomized non-blinded clinical trial was conducted on patients undergoing non-traumatic complex lumbar spine stabilization surgeries at the Chamran Hospital, affiliated to Shiraz University of Medical Sciences, from February to September 2019. The study protocol was ethically approved by the local committee (IR.SUMS.MED.REC.1396.125) and informed written consent was obtained from all participants.

Study population

The trial was performed on patients aged 40 to 75 years with American Society of Anesthesiologists (ASA) physical status I to II who were candidates for complex lumbar spine stabilization surgery with an appropriate mental capacity to cooperate. Those with other chronic pain syndromes, non-degenerative spine pathologies, uncontrolled seizures, history of depression and anxiety, repaired spinal dura mater layer during the operation, severe coagulation disorders, opioids and other types of drug abuse and dependency, sensitivity to the study drugs, and psychosomatic pain disorders were excluded.

Sample size

Based on a previous study,[9] 14 patients were considered per group, with a mean difference of 20 mm on visual analog scale measurements for pain, standard deviation of 16, power of 0.90, and type I error of 0.05. Out of 47 eligible patients, 16 were excluded, and 31 eligible patients met the criteria to be enrolled. Case (n = 15) and control (n = 16) patients were randomly allocated through the permutation block randomization method, based on 15 blocks in 2 permutations (Fig. 1).

Study intervention

Prior to surgery, participants were assessed for using the preoperative pain score and instructed on how to use a PCA pump and the pain assessment tool (numerical rating scale [NRS]). The surgical procedures were all performed by two spine surgeons with comparable techniques accompanied by a single anesthesiologist. A similar drug protocol was followed for both the induction and maintenance phase of anesthesia in all participants: 0.15 mg.kg^{-1} midazolam, 2 μg.kg^{-1} fentanyl as premedication plus 0.15 mg.kg^{-1} morphine sulfate in induction and 1$-$1.2% isoflurane in 50:50 mixture of oxygen, and nitrous oxide for maintenance of anesthesia.

In the bupivacaine group, a 15-cm multiorifice tip catheter (InfilteraLong 600, PAJUNK, Geisingen, Germany) was subfascially placed at the end of the operation. After implantation and fixation, 30 mL of 0.25% bupivacaine (Bupivacain®, Mylan, 100 mg/20 mL vial, Delpharm, France) were injected through the catheter as a bolus dose. Then, the catheter was connected to an elastomeric infusion pump containing 0.25% bupivacaine, the infusion of which was started at a rate of 6 mL.h^{-1}. No catheter was inserted in the control group. Intravenous morphine infusion via the PCA pumps was started for both groups in the ward (bolus dose: 1 mg, lockout interval: 7 minutes, no baseline infusion).

Study assessments

In the recovery room, the time interval between the end of the operation and the first request for analgesic was recorded. Moreover, if conscious, the patient's pain intensity was assessed and recorded according to the NRS every 15 minutes (at 15-, 30-, 45-, and 60-minute time points) in static state. Only single modal analgesia with intravenous (IV) morphine was administered to relieve the pain. For NRS < 4 no intervention was made; but for 4 < NRS < 7, the patient received 1 mg IV morphine every 5 minutes considering the vital signs until pain intensity dropped below 4; and for NRS > 7, 2 mg IV morphine was administered until the pain score dropped below 7, and thereafter managed with
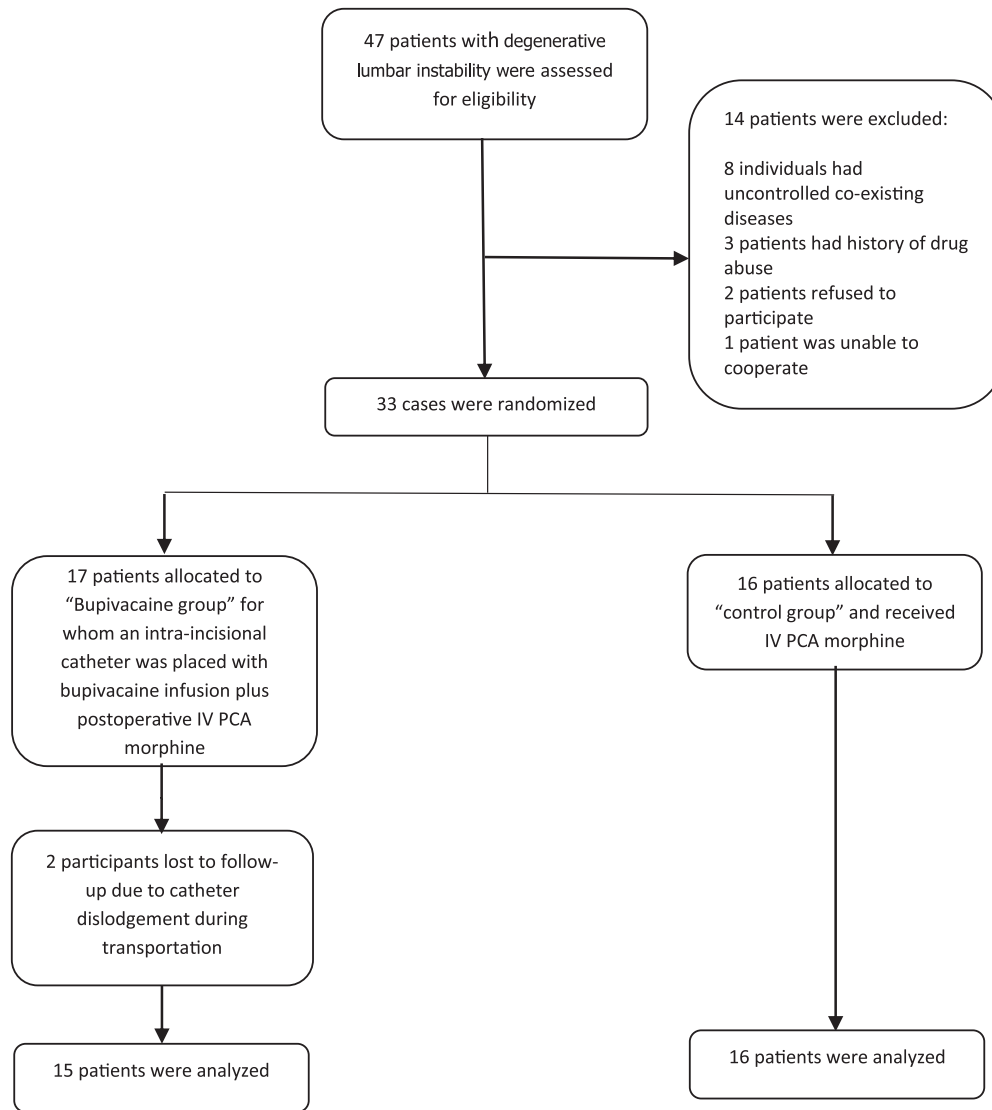
Figure 1 Flowchart of the study.

the protocol used for NRS between 4 and 7. The total amount of morphine consumed in the recovery room was recorded.

In the ward, the patient's pain intensity was hourly assessed and recorded during the first 6 hours, every 2 hours within the next 6 hours, and every 4 hours thereafter till the end of 24 postoperative hours. Morphine complications (respiratory depression, pruritus, urinary retention, nausea, and vomiting) were assessed every 4 hours during the study.

Data analysis

Data were statistically analyzed via SPSS software (version 21, SPSS Inc., IL, USA). Continuous variables were descriptively reported as mean $\pm$ standard error of mean (SEM) or median and interquartile range (IQR). Independent sample t-test and Mann-Whitney U test were used for continuous variables. Categorical variables were reported as numbers and percentages. The categorical outcomes were compared by the chi-square test. Repeated measure ANOVA was used for the data gathered over a period of time. $p < 0.05$ was considered statistically significant.

Results

The two groups were not significantly different in demographic variables (age, sex, weight, BMI, preoperative pain score) (Table 1). Significant differences existed between the two groups regarding recovery room morphine, ward morphine, and total morphine administration ($p < 0.001$). Yet, they were not different in terms of the time to the first request for analgesic (Table 2).

Pain score in the recovery room

Repeated measure ANOVA revealed a significant relation between the pain score in the recovery room and the time to the first analgesic request ($p = 0.002$), bupivacaine continuous injection ($p < 0.001$), and the interaction of these two variables (time $\times$ group) ($p = 0.002$). Considering the

Table 1 Patient demographic data.

Variables/Groups	Bupivacaine (n = 15)	Control (n = 16)	p
Age (year) (mean ± SEM)	55.93 ± 2.52	50.37 ± 2.24	0.109
Sex (female)	14 (93%)	11 (69%)	0.172
Weight (kg) (mean ± SEM)	73.80 ± 2.07	77.25 ± 2.15	0.258
BMI (mean ± SEM)	25.66 ± 0.93	26.61 ± 0.89	0.465
Preoperative pain score (mean ± SEM)	7.61 ± 0.74	6.52 ± 0.79	0.323

SEM, standard error of mean; BMI, body mass index.

Table 2 Postoperative morphine consumption.

Variables/Groups	Bupivacaine (n = 15)	Control (n = 16)	p
Time to the first request for analgesic (min)	30 (15-30)	15 (10-26)	0.225
Recovery room morphine (mg)	1.73 ± 0.27	5 ± 0.41	< 0.001
Ward morphine (mg)	5.60 ± 0.80	11 ± 0.97	< 0.001
Total morphine consumption (mg)	7.33 ± 0.93	16 ± 0.88	<0.001

significant interaction effect, the Mann-Whitney U test was performed to assess each time independently. Accordingly, the bupivacaine group had a lower pain score than the control group on all time-points in the recovery room (Fig. 2).

Pain score in the ward

Similarly in the ward, the pain score was found to be significantly related to the time to the first analgesic request ($p < 0.001$) and bupivacaine continuous injection ($p = 0.001$); however, the interaction between these two variables (time × group) was not statistically significant ($p = 0.494$). Using independent sample t-test to compare the pain scores (NRS) in the ward at each time-point showed significant differences between the two groups mostly at the first ($p < 0.001$) and second ($p = 0.002$) measurements in the ward (Fig. 3).

Drug-related complications

Neither group showed any drug-related complications such as seizures, arrhythmia, tinnitus, lightheadedness, and dizziness. Only one patient in the case group experienced nausea and vomiting at 4, 8, and 12 hours after the ward admission. The same patient experienced hypotension 4 hours after being transferred to the admission ward. Overall, the two groups were not significantly different regarding the drug-related side effects ($p = 0.707$).

Discussion

Relieving the inevitable severe postoperative pain is a serious concern in patients undergoing spinal deformity surgeries and spine stabilization.[17,18] Acute postoperative pain can have adverse consequences such as delayed wound healing, higher risk of infection, long-term hospitalization, readmission, and cardiovascular complications.[19,20] This randomized clinical trial revealed that at all time-points of the first 24 postoperative hours, the mean pain intensity was lower in patients on continuous injection of bupivacaine through an intra-incisional catheter than in those without catheter implantation; the differences being more prominent during the first postoperative hours. Since the mean preoperative pain score was not significantly different between the two
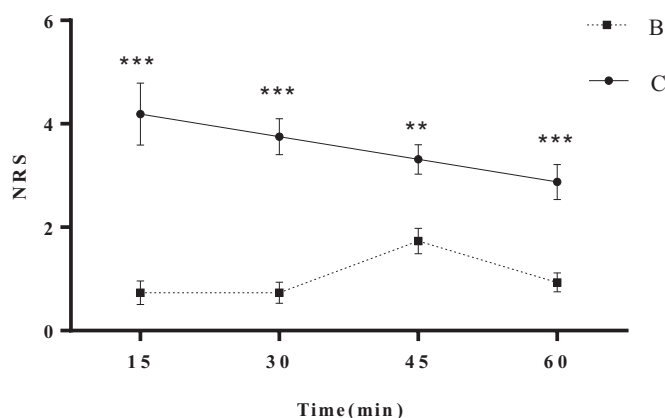
Figure 2 Pain intensity in the recovery room (*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$).
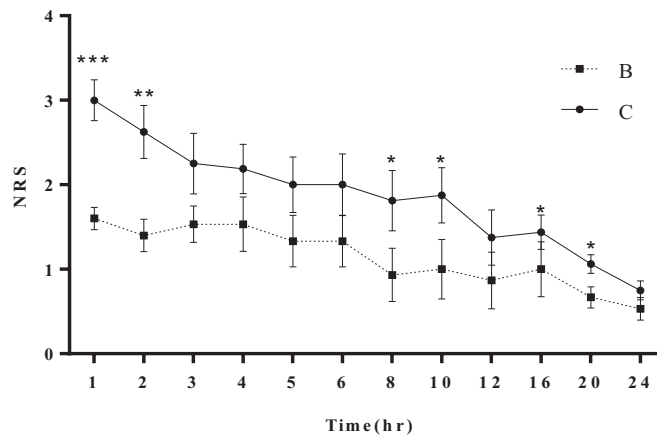
Figure 3 Pain intensity changes during the first 24 postoperative hours (*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

groups, it was not considered as an intervening effective factor.

While the present study aimed to extend postoperative analgesia beyond the effect of a bolus dose of local anesthetic injection, successful pain control was achieved in the period of efficacy of a single-shot injection (the bolus dose). This could be due to the inadequate dose of the running infusion and the wide extent of the surgical incision for this rate of infusion. Increasing the infusion rate might compensate for that; however, the total infusion dose should be regarded. The significant difference in pain intensity recorded in the recovery room which lasted for two hours after transferring to the ward might be attributed to the lower morphine requirement during the recovery room stay in the study group.

The efficacy of such a protocol has also been demonstrated in similar studies as follows. In a study by Bianconi et al.,[21] 38 patients scheduled for spinal stabilization received either intravenous morphine or 0.5% ropivacaine through an intra-incisional catheter. They detected that compared to morphine, ropivacaine significantly decreased pain intensity, analgesic need (diclofenac and tramadol), postoperative blood loss, and the length of hospitalization, with no side effects reported. Their results confirmed that the injection of ropivacaine into the surgical wound through a catheter and its continuous infusion could efficiently alleviate the postoperative pain of spine stabilization.

Xu et al.[22] found no significantly different pain intensity between the patients receiving ropivacaine injection through a catheter into the spinal thoracolumbar surgical wound and those receiving intravenous flurbiprofen, pentazocine, and palonosetron; although, ropivacaine was associated with significantly less nausea, vomiting, and chronic pain. Ali et al.[23] and Manan et al.[24] reported that injection of bupivacaine into the wound site significantly reduced the pain intensity after laparoscopic cholecystectomy.[23] Seelam et al.[25] noted that US-guided erector spinae plane block with bupivacaine in patients undergoing mastectomy resulted in less postoperative morphine consumption and significant postoperative pain relief, as compared with the control group.[25]

Being one of the main drugs for postoperative pain relief, morphine has side effects, and plausible drug-dependency in terms of long use of morphine makes the reduction of postoperative morphine prescription a crucial concern.

This study was strong for being a randomized clinical trial following CONSORT guidelines; however, it was not blinded and had a limited budget for the cost of catheters. Previous similar studies assessed a single-shot bupivacaine wound infiltration or continuous ropivacaine catheter wound infusion in more simple surgeries such as laminectomy. Whereas, the present study was focused on complex spinal fusion surgeries, not single-shot bupivacaine infiltration, and also assessed postoperative pain in continuous bupivacaine wound catheter infusion over 24 postoperative hours. On the other hand, previous studies using medications such as ropivacaine mentioned the high costs; whereas, the present study was superior due to using bupivacaine, which is economically cost-effective and reasonable for the patients. Although the sample size was statistically sufficient to interpret the data, further studies with a larger sample size are recommended.

Conclusion

With respect to the present findings, it can be concluded that using bupivacaine can reduce more efficiently the postoperative pain than morphine, at least in the early postoperative hours, and consequently reduce morphine consumption postoperatively. Continuous injection of bupivacaine through a catheter into a surgical wound to reduce the postoperative pain intensity in non-traumatic complex lumbar spine stabilization surgeries can be considered as a part of an opioid-sparing analgesic protocol.

Conflict of interests

The authors declare no conflicts of interest.

Acknowledgments

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