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ORIGINAL ARTICLE

Pre-emptive infiltration of levobupivacaine is superior to at-closure administration in lumbar laminectomy patients

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Abstract This is a prospective, randomized, controlled trial that compared the efficacy of different protocols of local tissue infiltration with levobupivacaine or levobupivacaine-methylprednisolone at the surgical site for pain relief after lumbar discectomy. The objective of the study was to determine the efficacy of preemptive wound infiltration with levobupivacaine and levobupivacaine-methylprednisolone at the surgical site for pain relief. Patients usually suffer significant pain after lumbar discectomy. Wound infiltration with local anesthetics with or without corticosteroids is one method to address this. A total of 100 patients were randomly allocated to five equal groups as follows: Group I had the musculus multifidi near the operated level infiltrated with 30 mL 0.25% levobupivacaine and 40 mg methylprednisolone just before wound closure; Group II had the same region infiltrated with 30 mL 0.25% levobupivacaine alone before closure; Group III had this region infiltrated with 30 mL 0.25% levobupivacaine and 40 mg methylprednisolone before the incision was made; in Group IV this region was infiltrated with 30 mL 0.25% levobupivacaine alone before incision; and in Group C (controls) this region was infiltrated with 30 mL 0.9% NaCl just before wound closure. Demographics, vital signs, postoperative pain scores and morphine usage were recorded. All four treatment groups showed significantly better results than the control group for most parameters. The treated groups had lower parenteral opioid requirements after surgery, lower incidences of nausea and shorter hospital stays. Further, the data indicate that, compared with infiltration of these drugs at wound closure, preemptive injection of levobupivacaine or levobupivacaine-methylprednisolone into the muscle near the operative site provides more effective analgesia after lumbar discectomy. Our data suggest that preemptive infiltration of the wound site with levobupivacaine alone or combined with methylprednisolone provides effective pain control with reduced opiate dose after unilateral lumbar discectomy.

Keywords Preemptive analgesia · Wound infiltration · Lumbar discectomy · Levobupivacaine · Methylprednisolone

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Introduction

Many patients with lumbar disc surgery experience postoperative back pain. Pain intensity peaks during the first postoperative hours and usually declines over the following 2 days. Inadequate management of postoperative mild or severe pain leads to several pathophysiological changes in the pulmonary and cardiovascular systems [10, 11, 19]. In fact, pain can cause an increase in sympathetic tone, which impairs neuroendocrine and metabolic catabolism, and may impair normal muscle functioning [21].

Local tissue infiltration has long been established as a reliable pain relief technique. Previously, we have shown the efficacy of local tissue infiltration with bupivacaine and corticosteroid on postoperative pain control after lumbar discectomy [6]. However, no study has yet investigated the

efficacy of preemptive analgesia with levobupivacaine and/or corticosteroid infiltration in this patient group. Levobupivacaine is the pure S(−) enantiomer of racemic bupivacaine. In clinical use, levobupivacaine has been shown to be equally effective as bupivacaine at comparable doses and concentrations, and has been found to produce similar anesthetic characteristics [1, 8]. Furthermore, levobupivacaine has a lower risk of cardiovascular and central nervous system toxicity than bupivacaine [7].

The aim of this study is to assess the differences in the treatment of pain following lumbar discectomy using two different modes of local administration of two different treatments (levobupivacaine alone or levobupivacaine plus methylprednisolone). Specifically, each experimental treatment was locally administered in the muscle around the wound site before incision as well as after skin closure.

Materials and methods

The design for this prospective, randomized, double-blind study was approved by our institutional ethics committee, and written consent was obtained from each participant. The research was conducted between September 2006 and May 2007. Patients were included if they met the following criteria: scheduled for surgery under general anesthesia for unilateral lumbar disc herniation; first lumbar disc surgery; age 18–60 years; Association of American Anesthesiologists (ASA) classification I or II; and no benefit from a 4-week course of conservative treatment. The exclusion criteria were spinal stenosis, known allergy to local anesthetics, pregnancy or the use of systemic steroids. In total, 100 patients were enrolled.

Each individual was randomly assigned to one of five groups. The groups were as follows: Group I ($n = 20$) had the musculus multifidi near the operation site infiltrated with 30 mL of 0.25% levobupivacaine and 40 mg methylprednisolone just before wound closure; Group II ($n = 20$) had the musculus multifidi near the operation site infiltrated with 30 mL of 0.25% levobupivacaine alone just before closure; Group III ($n = 20$) had the musculus multifidi near the operation site infiltrated with 30 mL of 0.25% levobupivacaine and 40 mg methylprednisolone just before the incision was made (preemptive analgesia with both drugs combined); Group IV ($n = 20$) had the musculus multifidi near the operation site infiltrated with 30 mL of 0.25% levobupivacaine alone just before incision (preemptive analgesia with levobupivacaine only); and Group C (controls, $n = 20$) had the musculus multifidi near the operation site infiltrated with 30 mL of 0.9% NaCl just before wound closure.

In the operating theater, each patient was prepared for continuous noninvasive blood pressure monitoring, peripheral pulse oxymetry, and electrocardiography. Each individual was premedicated with midazolam 0.03 mg/kg i.v. 3 min before induction. A standard anesthetic protocol was used (2–2.5 mg/kg propofol, 1–1.5 μg/kg fentanyl, 1 mg/kg rocuronium, and 1–1.5 mg/kg lidocaine). The maintenance anesthesia was 2% sevoflurane in a 40: 60 mix of oxygen and nitrous oxide, with bolus doses of rocuronium and fentanyl given as required until 45 min before the end of surgery. After surgery, each subject had access to i.v. patient-controlled analgesia (PCA) with morphine for 24 h (2 mg bolus, 10-min lock-out time and a 4-h dose limit of 0.4 mg/kg). Patients who developed postoperative nausea or vomiting received intramuscular injections of 10 mg metoclopramide. Also, if VAS scores were >5, 75 mg diclofenac was used as additional analgesic.

Perioperative data recorded

The collected patient demographic characteristics and features of the operation included age, sex, weight, ASA classification and duration of operation. The following patient vital signs were assessed: systolic blood pressure, diastolic blood pressure and pulse rate (PR) at induction and at 5, 10, 15, 30, 60 and 90 min intraoperatively.

Postoperative data recorded

The postoperative data parameters were recorded at 1, 4, 8, 16, 20 and 24 h after surgery by a pain clinic nurse who visited each patient. Additionally, the following vital signs were recorded: systolic blood pressure, diastolic blood pressure and PR.

Pain Visual Analogue Scale (VAS)

An 11-point VAS was used to assess pain levels. A VAS score of 0 indicated no pain, whereas 10 indicated the most severe pain imaginable.

Ramsay Sedation Scale [20]

A 6-point scale was used to assess sedation levels, with 1 indicating agitated, anxious; 2, cooperative; 3, only responds to commands; 4, strong response to glabellar tapping or noisy stimulants; 5, weak response to glabellar tapping or noisy stimulants; 6, no response.

Postoperative PCA parameters

The time of first analgesic demand, number of PCA demands, number of PCA boluses received, cumulative morphine dose for three separate periods (0–4, 4–12, and 12–24 h) and total morphine dose at 24 h were collected.

Table 1 Demographic characteristics of study and control groups

	Group I ($n = 18$)	Group II ($n = 19$)	Group III ($n = 19$)	Group IV ($n = 20$)	Group C ($n = 19$)
Age (year)	42.6 ± 9.7	44.8 ± 10.6	48.7 ± 10.2	42.3 ± 11.2	45.8 ± 10.9
Sex (male/female)	11/7	12/7	9/10	13/7	11/8
Height (cm)	169.8 ± 7.4	170.7 ± 8.2	167.7 ± 6.8	171.3 ± 7.9	166.4 ± 6.5
Weight (kg)	78.9 ± 14.3	81.9 ± 15.2	77.4 ± 13.1	76.2 ± 11.8	72.6 ± 11.2
ASA (I/II)	14/4	15/4	13/6	14/6	13/6
Operation time (min)	115.1 ± 26.7	108.4 ± 31.1	106.2 ± 29.8	117.7 ± 32.6	104.8 ± 28.4

Data are given as (n) or mean ±SD

Table 2 Postoperative results

	Group I ($n = 18$)	Group II ($n = 19$)	Group III ($n = 19$)	Group IV ($n = 20$)	Group C ($n = 19$)
First analgesic requirement (min)	38.6 ± 19.5*	42.2 ± 18.9*	62.7 ± 21.3†‡	60.6 ± 21†‡	27.3 ± 18.3
PCA demands (n)	16.3 ± 7.8†	15.8 ± 7.2†	12.3 ± 7.4†	13.2 ± 6.9†	37.3 ± 11.6
PCA boluses (n)	8.6 ± 3.2†	7.7 ± 3.3†	6.1 ± 2.7†	6.3 ± 2.6†	14.6 ± 5.3
Total morphine consumption at 24 h (mg)	16.8 ± 4.3†	15.1 ± 4.1†	11.7 ± 3.7†	12.1 ± 3.9†	27.6 ± 6.2
Hospital stay (h)	19.6 ± 2.8†	20.4 ± 2.4†	18.7 ± 2.2†	18.6 ± 1.9†	25.7 ± 2.1

Data are given as mean ± SD

* $P < 0.05$, compared with Group C

† $P < 0.001$, compared with Group C

‡ $P < 0.01$, compared with Groups I and II

PCA patient-controlled analgesia

Adverse effects

Adverse effects observed in this study included nausea, vomiting and steroid-related adverse effects (gastrointestinal bleeding, gastritis, delayed wound healing, Cushing's syndrome, etc.). Patients who were discharged within 24 h following surgery were telephoned at home and their pain scores and sedation scores were recorded.

Statistical analyses

Power analysis was performed at the design stage of our previous study. The authors estimated that there was a 0.85 probability (in SD) that a patient who received a local injection of levobupivacaine or levobupivacaine-methylprednisolone would report lower pain intensity on VAS scoring than a patient who received a local injection of saline solution. Assuming that the pain scores would be compared using the Wilcoxon's rank sum test with two-sided 10% level of statistical significance and 90% power, the authors calculated that at least 95 patients (19 per group) were required. Kruskal–Wallis, Chi-square, and Mann–Whitney U tests were used to analyze the data. P values <0.05 were considered to be statistically significant.

Results

There were no significant differences among the five study groups with respect to mean age, sex distribution, mean weight, proportions of ASA classifications and mean operating time (Table 1). There were also no significant differences among the groups with respect to mean arterial pressure (MAP) or mean PR before induction, during the operation or in the first 24 h after surgery ($P > 0.05$ for all). Two patients in Group I, and one patient in Groups II, III and V were excluded from the study.

The results for the postoperative data are presented in Table 2. Groups I through IV all had significantly longer mean times to first analgesic (PCA) demand than the control group ($P < 0.05$ for Groups I and II, and $P < 0.001$ for Groups III and IV). Furthermore, the mean time to first PCA demand in Group III and Group IV (preemptive analgesia with levobupivacaine-methylprednisolone and levobupivacaine alone) was significantly longer than the corresponding times for Groups I and II ($P < 0.01$ for both). There were no significant differences among the four medicated groups with respect to mean total numbers of PCA demands or mean numbers of PCA boluses delivered. However, Groups I through IV all had significantly lower values for PCA demands and PCA boluses delivered than Group C

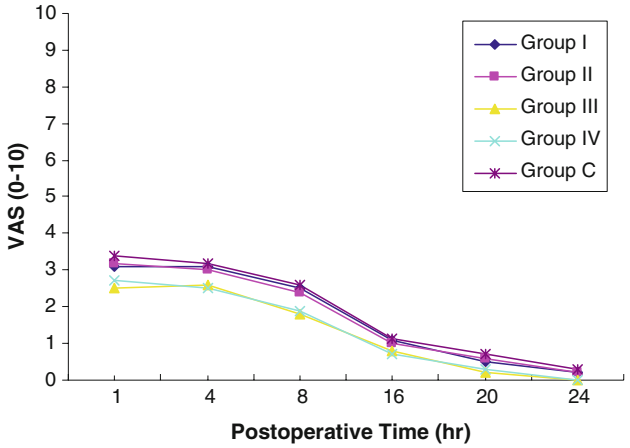

Fig. 1 VAS scores in postoperative 24 h after surgery

($P < 0.001$ for all). Similarly, there were no significant differences among the four medicated groups with respect to mean values for total morphine received in the first 24 h. However, the control group had significantly higher values for all these parameters than the treated groups ($P < 0.001$ for all). Although Groups III and IV had lower values of mean PCA demands, mean PCA boluses, and mean total morphine consumption compared to Groups I and II, these differences were found to be insignificant. The medicated groups also had statistically similar mean hospitalization times, whereas the mean hospital stay for Group C was significantly longer ($P < 0.001$ for all). The mean VAS scores for the five groups were similar to those shown in Fig. 1. No additional analgesics were required at all.

For all five groups, the mean Ramsay sedation score at each postoperative time point evaluated was 2 (cooperative). The numbers of patients who developed postoperative nausea in Groups I, II, III, IV and C were 4, 7, 5, 5 and 11, respectively. The control group had a significantly higher frequency of nausea compared to all other groups ($P < 0.05$ for all). The group incidence rates for postoperative vomiting were statistically similar.

Discussion

In our study, all four groups of lumbar discectomy patients who were treated with levobupivacaine or levobupivacaine-methylprednisolone (by preemptive or preclosure wound infiltration) showed significantly better results than the control group for most parameters. The treated groups had lower parenteral opioid requirements after surgery, lower incidences of nausea and shorter hospital stays. The data further indicate that, compared with infiltration at wound closure, preemptive injection of levobupivacaine or levobupivacaine-methylprednisolone into the muscle near the operative site provides more effective analgesia after lumbar discectomy.

Local tissue infiltration has long been established as a reliable pain relief technique, and interest in the use of this technique has been recently revived [14]. The main advantages of this technique are its simplicity, safety and low cost. The agent most widely used for this purpose is 0.25% bupivacaine. Injected corticosteroids also act against pain by inhibiting inflammation and therefore preventing the secretion of neuropeptides that stimulate thin nerve fibers. These drugs inhibit both the early inflammatory response (edema, fibrin formation, capillary dilatation, leukocyte aggregation) and the late effects of this process (proliferation of capillaries and fibroblasts, collagen formation and scarring) [5, 16].

It has been suggested that preoperative infiltration of local anesthetics provides a greater reduction in postoperative pain than perioperative or postoperative infiltration. According to this hypothesis, local infiltration and the resulting nerve impulse block prevent nociceptive impulses from reaching the CNS and suppress the sustained state of hyperexcitability responsible for intense postoperative pain [12].

Peripheral tissue injury results in two kinds of modification to the responsiveness of the CNS: a peripheral and a central sensitization. The central sensitization leads to an increased excitability of spinal cord neurons that is triggered by nociceptive afferent inputs. This sensitization, caused by operative tissue damage, results in an increase in the response to pain [22]. The local infiltration of anesthetic blocks C-fiber input to the dorsal horn and may thereby inhibit central sensitization. Bisgaard et al. [2] have shown that a combined somatovisceral ropivacaine blockade reduces overall pain, incisional pain and morphine requirements in patients after laparoscopic cholecystectomy. This group also demonstrated that local infiltration with ropivacaine reduces incisional pain without causing deep intraabdominal pain.

The use of levobupivacaine was addressed by Bay-Nielsen et al. [1], who found that there was no difference between the use of 50 mL of 0.25% levobupivacaine and the use of an equivalent amount of 0.25% bupivacaine in effecting pain relief after inguinal hernia repair. We were unable to locate any other clinical studies investigating local tissue infiltration with levobupivacaine as an anodyne for the pain of lumbar discectomy. The recommended dose of levobupivacaine for incisional analgesia is 150 mg. To avoid local and systemic toxicity, we used only 75 mg of this agent for tissue infiltration.

Local anesthetic agents have been widely used in many surgical operations to reduce incisional pain. In 1979, Mullen and Cook [17] reported that the use of intramuscular bupivacaine during lumbar discectomy resulted in a marked reduction of postoperative back pain. In a double-

blind randomized trial, Milligan et al. [15] described 60 patients in whom bupivacaine was beneficial, based on VAS scores and narcotic use in the first 24 h after lumbar discectomy. In a similar study by Cherian et al. [4] bupivacaine was concluded to be beneficial because there were significant differences between groups in the time to the first postoperative use of narcotic analgesic.

Numerous studies [9, 13, 18] have demonstrated that wound infiltration with local anesthetics and/or different forms of cortisone for lumbar discectomy can reduce requirements for rescue analgesics in the postoperative period. However, our results specifically indicate that administering local anesthetics (alone or combined with steroid) to paravertebral and cutaneous-subcutaneous tissues at the time of incision (preemptively) offers the best pain relief after lumbar discectomy.

Side effects like gastrointestinal hemorrhage, gastritis, delayed wound healing, Cushing's syndrome, glucose intolerance and hypertension associated with short-term corticosteroid use are generally mild and completely reversible. None of our patients developed these side effects. As Glasser et al. [9] indicated, the likelihood of such adverse effects occurring in this setting is low because only a small steroid dose is administered. Avascular necrosis is a rare but severe and dose-dependent side effect seen in long-term corticosteroid use [3]. As our patients received the steroid treatment on a single occasion, the risk of such side effects was very low.

Conclusion

Preemptive administration of levobupivacaine or levobupivacaine-methylprednisolone to the paravertebral muscles in patients who undergo lumbar discectomy provides effective analgesia, if started immediately after the operation. These individuals experience significantly less pain in the early postoperative period compared with patients who receive no local anesthetics or steroids. Preemptive infiltration with levobupivacaine or levobupivacaine-methylprednisolone offers no advantage over preclosure, administration with respect to hospitalization time or supplemental opioid requirements, although preemptive infiltration groups had a significantly longer first analgesic requirement following the operation.

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