The Spine Journal 000 (2023) 1–8

Clinical Study

Effectiveness and safety of intrathecal morphine for percutaneous endoscopic lumbar discectomy under low-dose ropivacaine: a prospective, randomized, double-blind clinical trial

Lei Yue, MD[a,#], Feng Zhang, MD[b,#], Guanzhang Mu, MD[a], Meixia Shang, MS[c], Zengmao Lin, MD[b,**], Haolin Sun, MD[a,*]

[a] *Department of Orthopedics, Peking University First Hospital, 8th Xishuku Ave, Xicheng District, Beijing, 100034, China*
[b] *Department of Anesthesiology, Peking University First Hospital, 8th Xishuku Ave, Xicheng District, Beijing, 100034, China*
[c] *Department of Medical Statistics, Peking University First Hospital, 8th Xishuku Ave, Xicheng District, Beijing,100034, China*

Received 3 January 2023; revised 6 February 2023; accepted 2 March 2023

Abstract

BACKGROUND CONTEXT: Percutaneous endoscopic lumbar discectomy (PELD) is a surgical setting that requires minimal motor impairment. Low-dose spinal ropivacaine induces little motor blockade and could be ideal for maintaining safety of PELD, but its analgesic efficacy is questionable. An adjunct analgesic approach is needed to maximize the benefits of low-dose spinal ropivacaine for PELD.

PURPOSE: This study aimed to explore the effectiveness and safety of 100 μg intrathecal morphine (ITM) as an adjuvant analgesic method for PELD under low-dose spinal ropivacaine.

STUDY DESIGN: A double-blind, randomized, placebo-controlled trial. Trial registration: ChiCTR2000039842 (www.chictr.org.cn).

SAMPLE: Ninety patients scheduled for elective single-level PELD under low-dose spinal ropivacaine.

OUTCOME MEASURES: The primary outcome was the overall intraoperative visual analogue scale (VAS) score for pain. Secondary outcomes were intraoperative VAS scores assessed at multiple timepoints; intraoperative rescue analgesic requirement; postoperative VAS scores; disability scale; patients' satisfaction with anesthesia; adverse events; and radiographic outcomes.

METHODS: Patients were randomized to receive low-dose ropivacaine spinal anesthesia with (ITM group, n=45) or without (control group, n=45) 100 μg ITM.

RESULTS: The overall intraoperative VAS score in the ITM group was significantly lower than that in the control group (0 [0, 1] vs 2 [1, 3], p<.001). During operation, the VAS scores at cannula insertion, 30 minutes after insertion, 60 minutes after insertion, and 120 minutes after insertion were all significantly lower in the ITM group (all p<.05). Less patients in the ITM group required rescue analgesia during operation compared with those in the control group (14% vs 42%, p=.003). The VAS score for back pain in the ITM group was lower than that in the control group at 1 hour, 12 hours, and 24 hours postoperatively. Besides, the satisfaction score in the ITM group was significantly higher than that in the control group (p=.017). For adverse events, 8/43 of ITM and 1/44 of control participants experienced pruritus (p=.014), with a relative risk (95% confidence interval) of 8.37 (1.09–64.16). The incidence of other adverse events was similar between the two groups. Of note, respiratory depression occurred in one ITM-treated patient.

FDA device/drug status: Not applicable.

Author disclosures: ***LY:*** Nothing to disclose. ***FZ:*** Nothing to disclose. ***GM:*** Nothing to disclose. ***MS:*** Nothing to disclose. ***ZL:*** Nothing to disclose. ***HS:*** Grant: Interdisciplinary clinical research project of Peking University First Hospital (No. 2021CR31) (C).

*Corresponding author. Department of Orthopedics, Peking University First Hospital, 8th Xishuku Ave, Xicheng District, Beijing 100034, China. Tel.: +(86) 010 8357-2655.

**Corresponding author. Department of Anesthesiology, Peking University First Hospital, 8th Xishuku Ave, Xicheng District, Beijing, 100034, China. Tel.: +(86) 010 8357 5138.

E-mail addresses: linzengmao@163.com (Z. Lin), sunhaolin@vip.163.com (H. Sun).

[#] Lei Yue and Feng Zhang contributed equally to this work and share first authorship.

https://doi.org/10.1016/j.spinee.2023.03.001

CONCLUSION: The addition of 100 μg ITM to low-dose ropivacaine appears to be effective in analgesia without compromised motor function for PELD; however, ITM increased the risk of pruritus and clinicians should be vigilant about its potential risk of respiratory depression.

Keywords: Analgesia; Endoscopy; Intrathecal injection; Morphine; Percutaneous discectomy

Introduction

Lumbar disc herniation (LDH) is a leading cause of low back and radicular pain, which are common causes of chronic pain and major contributors to disabling conditions globally [1−3]. Though most patients respond well to nonsurgical treatment, inadequate resolution of symptoms to conservative measures may result in surgery in 10% of the patients [4]. Thanks to the development of minimally invasive spine surgery (MISS), LDH patients undergoing spine surgery could now benefit from a smaller incision, faster recovery, and fewer surgical complications. Percutaneous endoscopic lumbar discectomy (PELD) is a well-proven MISS approach for LDH, and studies have shown that PELD reduces complication risk while achieves similar clinical results compared with traditional open surgery [5,6].

The primary concern for successful PELD is to avoid nerve damage caused by surgical instruments; hence, PELD is often performed under awake anesthesia, rather than general anesthesia, to receive timely feedback of the lower extremity movement during operation [7]. Evidence has shown that epidural anesthesia provides better analgesia for endoscopic spine surgery compared with local anesthesia [8,9] , and spinal anesthesia theoretically could further reduce the risk of motor blockade and increases analgesic efficiency in comparison to epidural anesthesia [10,11]. Furthermore, previous studies demonstrated that low-dose ropivacaine (0.1%−0.15%) to be effective in reducing the risk of motor blockade, but inadequate in perioperative analgesia [12,13]. Therefore, an adjunct analgesic approach is needed to maximize the benefits of low-dose spinal ropivacaine for PELD.

Intrathecal morphine (ITM), first used in cancer pain management in 1979, has been now applied in various surgical scenarios including open spine surgery [14,15]. ITM requires lower effective dosage and lasts longer compared with systemic morphine [16]. The efficacy and side-effect risk of ITM are both dose-related, and previous systematic reviews have suggested 100 μg may be the optimal dosage of ITM [17,18]. The aim of this study was to investigate the effectiveness and safety of 100 μg ITM as an adjuvant analgesic method for PELD with low-dose spinal ropivacaine.

Materials and methods

Trial design

This is a prospective, randomized, double-blind, placebo-controlled study conducted in accordance with the Declaration of Helsinki. Each participant was fully informed and signed an informed consent to participate. The study was approved by the Institution Review Board of Peking University First Hospital (No. 2020-289) and prospectively registered at Chinese Clinical Trial Registry (identifier: ChiCTR2000039842). The protocol of this trial was prospectively published [19].

Participants

This trial was conducted at Peking University First Hospital, Beijing, China. The inclusion criteria were as follows: (1) patients' age at least 18 years; (2) symptomatic LDH confirmed by symptoms, signs, and magnetic resonance imaging (MRI); (3) undergoing single-segment PELD with low-dose intrathecal ropivacaine; (4) American Society of Anesthesiologists (ASA) score $\leq$ 3. The exclusion criteria were as follows: (1) morphine use history within 3 days before surgery; (2) contraindications for morphine use or spinal anesthesia; (3) respiratory disorders (obstructive sleep apnea syndrome, chronic obstructive pulmonary disease, asthma, or chronic cough); (4) obesity (BMI $\geq$30 kg/m^2); (5) mental incapacity or legal incompetence; (6) pregnancy or lactation in women.

Randomization and allocation

After giving informed consent, the participants were randomly assigned into either the ITM or the control (CON) group with an equal allocation ratio (1:1) with a block size of 4 by an independent statistician (SMX) using SAS statistical package version 9.4 (SAS Institute, Cary, NC, USA). Each patient's allocation was concealed in a sequentially numbered, sealed, and opaque envelope. The envelopes were not opened until the patient arrived at the operation room by a senior anesthetist (LZM), the only researcher aware of the allocation. The patients, surgeons, investigators, nurses, outcome assessors, and data analysts were all blinded to group allocations.

Intervention

Before spinal anesthesia, the skin of the back was routinely prepared and infiltrated with 2 mL of 1% lidocaine. The subarachnoid space puncture was performed with a 25-gauge pencil-point spinal needle (Tuoren, Xinxiang, China), following confirmation of the return of clear, free-flowing cerebrospinal fluid. All patients received hypobaric

spinal anesthetic solution which contained ropivacaine 7.5 mg (0.125%, 6 mL). Next, 100 μg of morphine diluted in 2 mL of 0.9% saline was administered intrathecally in the ITM group, while 2 mL of 0.9% saline was administered intrathecally in the CON group. Supplementary Appendix 1A–B illustrates the implementation and mechanism of intrathecal administration of the drugs. Then, the patients changed to a prone position and the PELD procedure was performed. Intravenous flurbiprofen axetil was provided as rescue analgesia during and after the operation. No sedative drugs were used in this study due to concerns about their respiratory depressive effects. The surgeries of all participants were performed by the same surgeon (SHL), who has experience with more than 600 cases of PELD.

Outcome assessment

The primary outcome was the overall intraoperative pain intensity reported by the patients on a 10-point visual analog scale (VAS) for pain right after the operation ended (Supplementary Appendix 1C). Secondary outcomes were intraoperative VAS scores assessed at every 30 minutes since the insertion of the working cannula; intraoperative analgesic requirement; postoperative low-back and lower extremity VAS scores at rest and at movement evaluated at 1 hours, 12 hours, 24 hours, 72 hours, and 1 month after operation; Owestry Disability Index (ODI) evaluated at 1 month after surgery; overall satisfaction with anesthesia using a 5-point Likert scale; radiographic parameters; and other in-hospital characteristics.

Predefined ITM-related AEs were respiratory depression, nausea or vomiting, pruritus, hypotension, or urinary retention. To ensure safety, continuous electrocardiography, noninvasive blood pressure, and pulse oximetry was performed in 12 hours postoperatively on all participants. Besides, we also recorded anesthetic AEs, surgical AEs, and other AEs during the 1-month follow-up period. In addition, the severity of AEs was graded from 0 to 5 in accordance with the US Department of Health and Human Services (HHS) [20].

Statistical analysis

All data were anonymized, and analyzed using SPSS, version 27.0 (IBM, Armonk, NY, USA). All analyses were on an intention-to-treat (ITT) basis. The Shapiro–Wilk test was applied to verify the normality of the continuous variables. The continuous variables were presented as the mean and standard deviations (SDs) if normally distributed, or the median and interquartile range if not normally distributed. The independent-sample *t* test was used for continuous variables with a normal distribution, while the Mann-Whitney *U* test was used for data without a normal distribution. Categorical variables were described as frequencies and percentages, and were analyzed with Fisher's exact test or the chi-square test. Multiple imputation was applied for dealing with missing data. A two-sided p value lower than .05 was considered statistically significant.

The sample size calculation was based on the results of our pilot study, which showed that the overall intraoperative VAS in the ITM group was 0.60 ± 0.55 and the VAS in the placebo group was 1.00 ± 0.71 (Supplementary Appendix 2). Considering a drop-out rate of 10% (including failed spinal anesthesia), a sample size of 45 patients per group would be sufficient with a statistical power of 80% and a false-positive error rate of two-sided p-value of .05.

For the primary outcome, we performed three prespecified subgroup analyses based on age, symptom length and gender. In addition, the sensitivity analyses for the primary outcome were conducted by excluding data from patients who required intraoperative rescue analgesia.

Moreover, the evaluation of the blinding implementation was performed by comparing the proportion of participants who speculated that they were treated with ITM between the two groups, and blinding was considered successful if no significant difference was observed.

Results

Participants

The flow of the patients through the trial is presented in Fig. 1. Between November 2020 and March 2022, a total of 152 patients undergoing single-segment PELD in our center were screened. Among 105 eligible patients, six patients refused to participate; nine patients changed to receive other surgery or anesthesia. Finally, 90 patients were randomly assigned to the ITM group (n=45) or the CON group (n=45). During the follow-up process, two patients in the ITM group dropped out due to the failed spinal anesthesia, and one patient in the CON group discontinued study due to early revision surgery. Protocol deviation was considered unserious (Supplementary Appendix 3C).

Overall baseline and clinical characteristics of the patients were similar between the ITM and CON groups (Table 1). The operative data were similar between the two groups, except for the distribution of operated spinal levels (p=.032) (Supplemental Appendix 4). Moreover, the MRI characteristics of the symptomatic segment, including protrusion location, protrusion size, Pfirrmann degeneration grade, Modic change, high intensity zone, Schmol's node, and facet tropism, were similar among the two groups (Supplementary Appendix 5).

Primary outcome

The overall intraoperative pain intensity in the ITM group was significantly lower than that in the CON group (0 [0, 1] vs 2 [1, 3], p<.001)] (Fig. 2). Similar to the complete cohort, the overall intraoperative VAS score in the ITM group was significantly lower than that in the CON group in most of the subgroup analyses (p<.05), except in patients who experienced a shorter symptom length (1 [0,

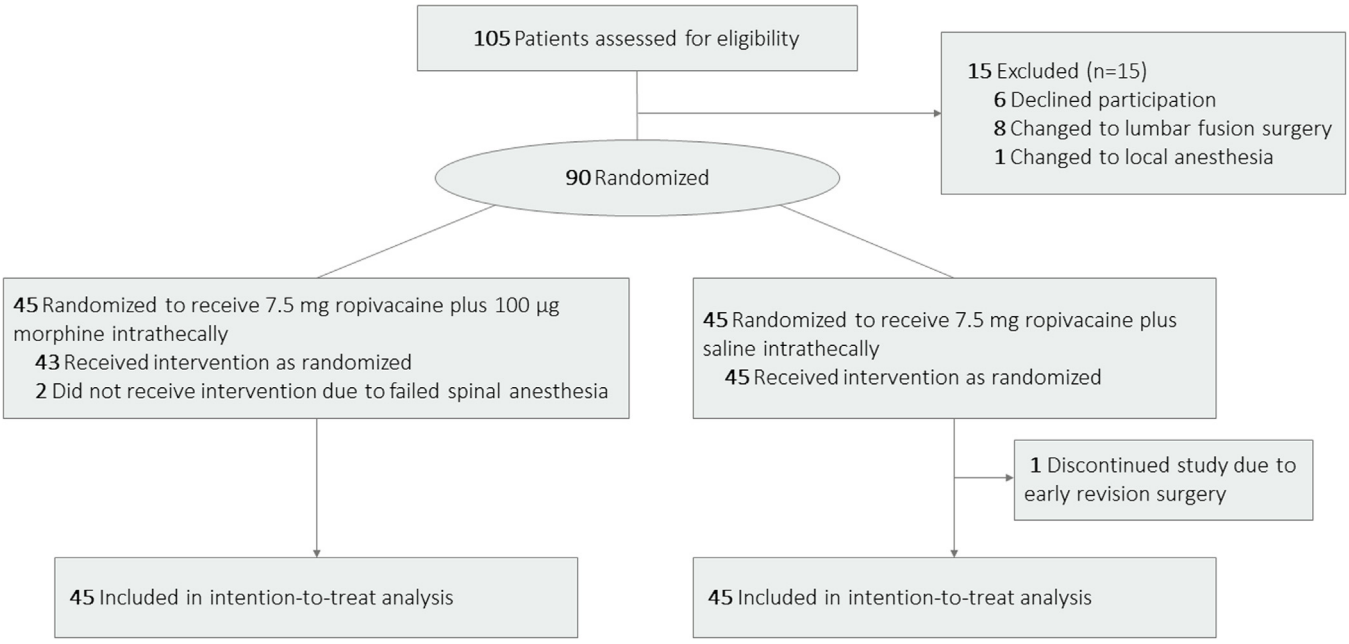

Fig. 1. Patient Consolidated Standards of Reporting Trials (CONSORT) flow diagram Through 1-Month Follow-up. Two participants in the morphine group experience failed spinal anesthesia and changed to local anesthesia. Early disc re-herniation and additional open decompression surgery occurred in one participant in the control group.

1.5] vs 1.5 [1, 2.5], p=.052). Sensitivity analyses produced a similar result for the primary outcome (Supplementary Appendix 6 and 7).

Secondary outcomes

The VAS scores at cannula insertion, 30 minutes after insertion, 60 minutes after insertion, and 120 minutes after insertion in the ITM group were significantly lower than those in the CON group (all p<.05) (Supplementary Appendix 8). The proportion of patients requiring intraoperative rescue analgesics was significantly lower in the ITM group than in the CON group (14% vs 42%, p=.003), with the relative risk (95% confidence interval [CI]) of 0.33 (0.15 −0.75). The time to the first rescue analgesics during operation was longer in the ITM group than in the CON group, but the difference was not significant (97.50 [67.50, 108.75] minutes vs 67.00 (60.00, 75.00) minutes, p=.088).

At postsurgical follow-ups, the back VAS scores were significantly lower in the ITM group compared with the CON group at 1 hour, 12 hours, and 24 hours, at both rest and movement (all p<.05); however, no differences were observed at follow-ups after 24 hours (all p>.05). The leg-pain intensity was similar between the two groups at most follow-up time points, except at 12 hours postoperatively at movement (p=.01) (Supplementary Appendix 9).

At 1-month follow-up, the ODI score was similar between the two groups (11.11 [4.44, 17.78] vs 11.11 [2.22, 17.61], p=.749). In addition, the satisfaction score was significantly higher in the ITM group in comparison to the CON group (p=.017).

The radiographic parameters at 24 hours after surgery, including lumbar lordosis, intervertebral disc angle, and coronal Cobb angle, were all similar between the ITM group and the CON group (Supplementary Appendix 10). Supplementary file 2 shows the normality test of continuous variables in this study.

Adverse events

All the five predefined opioid-related AEs occurred in this study. The incidence of pruritus was significantly higher in the ITM group than in the CON group (19% vs. 2%, p=.014), with the relative risk (95% CI) of 8.37 (1.09 −64.16); however, the incidence of pruritus requiring medication was not significantly different between the ITM group and the CON group (5% vs 0%, p=.236). Post-hoc univariate risk factor analysis showed that the risk of pruritus correlated with high BMI and smoking. Compared with the CON group, the ITM group showed higher incidence of nausea or vomiting (30% vs 16%, p=.101), hypotension (5% vs 2%, p=.612), urinary retention (4% vs 2%, p=.612), and respiratory depression (2% vs 0%, p=.489); however, none of the above results differed statistically.

There was no significant difference in the incidence of motor block between the ITM group and the CON group (2.33% vs 4.44%, p=1.000). The incidence of other anesthetic AEs, including shivering, transient neurologic symptoms, and transient perianal numbness, was also similar between the groups. One patient in the CON group suffered from acute radicular pain and reherniation of the operated disc was found on MRI at 14 hours after PELD, and

Table 1
Baseline demographic and clinical characteristics of the study

	ITM (n=45)	CON (n=45)	p value
Age, median (IQR), years	39 (31, 43)	36 (32.5, 42.5)	.734*
Gender, No. (%)			.827†
Women	17 (38)	16 (36)	
Men	28 (62)	29 (64)	
BMI, mean (SD), kg/m^2	24.57±2.82	25.06±3.67	.485‡
Symptom length, No. (%)			.375*
< 1 mo	4 (9)	5 (11)	
< 3 mo	7 (16)	10 (22)	
≥ 3 mo	34 (76)	30 (67)	
Smoking, No. (%)	9 (2)	14 (31)	.227†
Alcohol, No. (%)	6 (13)	6 (13)	1.000†
ASA classification, No. (%)			.094*
I, healthy	7 (16)	16 (36)	
II, mild systematic disease	38 (84)	28 (62)	
III, severe systematic disease	0 (0)	1 (2)	
Preoperative self-reported clinical outcomes			
Back VAS score at rest, median (IQR)	1 (0, 3)	2 (0, 3)	.299*
Back VAS score at movement, median (IQR)	3 (1, 4)	4 (1, 6)	.290*
Lower extremity VAS score at rest, median (IQR)	3 (2, 4)	3 (2, 5)	.873*
Lower extremity VAS score at movement, mean (SD)	5.07±2.36	4.84±2.58	.671‡
ODI score, median (IQR), %	48.89 (30.56, 68.90)	28.89 (26.67, 43.11)	.003*

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; CON, control; IQR, interquartile range; ITM, intrathecal morphine; ODI, Owestry Disability Index; SD, standard deviation; VAS, visual analog scale.

* Mann-Whitney *U* test.

† Chi-square test or Fisher exact test.

‡ Independent t-test.

emergent open decompression surgery was then performed (HHS grade 3). One patient in the ITM group was rehospitalized for symptom recurrence, but not surgery (HHS grade 3). Table 2 shows the details of AEs found in the current trial.

Blinding assessment

At the last follow-up, 33 (77%) participants in the ITM group speculated that they had been given the active treatment compared with 29 (66%) of placebo-assigned participants (p =.264). Thus, blinding for patients was considered successful in our study.

Discussion

In this prospective, randomized, double-blinded, placebo-controlled trial, 100 μg ITM compared with placebo treatment significantly reduced intraoperative and postoperative pain intensity within 24 hours, and reduced the intraoperative rescue analgesia requirements for PELD under low-dose spinal ropivacaine. Motor function was well-preserved in most patients and no nerve injury was observed in all participants. However, 100 μg ITM significantly increased the risk of pruritus, and respiratory depression occurred in one patient in ITM group.

As mentioned above, PELD is preferred to be performed in the presence of retained motor function. Although Panni et al. [21] reported that median effective dose (ED50) for spinal ropivacaine was 16.4 mg, 18% of patients experienced motor block in their study, which makes the dosage intolerable for PELD. Previous studies have shown that 0.125% ropivacaine has little effect on motor function, but its anesthetic efficacy is controversial [22–24]. We applied 6 mL of 0.125% spinal ropivacaine and found that motor block only occurred in 3.1% of the studied population, while ITM did not increase the risk of motor blockade. However, 42% patients in the CON group required additional analgesics during operation, indicating that anesthesia may be insufficient. By contrast, the addition of 100 μg ITM significantly reduced intraoperative analgesic requirements and pain intensity intraoperatively and up to 24 hours postoperatively. Previous meta-analysis revealed that ITM significantly reduced pain scores at the initial 12 to 24 hours and postsurgical analgesic consumption for spinal fusion surgery [15]. In addition, Morselii et al. [25] reported that 100 μg ITM significantly improved pain intensity in the first 24 hours postoperatively compared with 5 mg of intravenous morphine for minimally invasive fusion surgery. It is therefore reasonable to conclude that 100 μg ITM is effective for PELD under low-dose spinal ropivacaine, and its therapeutic time window is from the injection to 24 hours afterwards.

The cephalad flow of morphine to the receptors in the medulla may lead to unwanted opioid-related side-effects, which have caused concerns among physicians and limited the clinical use the ITM. Small morphine dose aside, all of

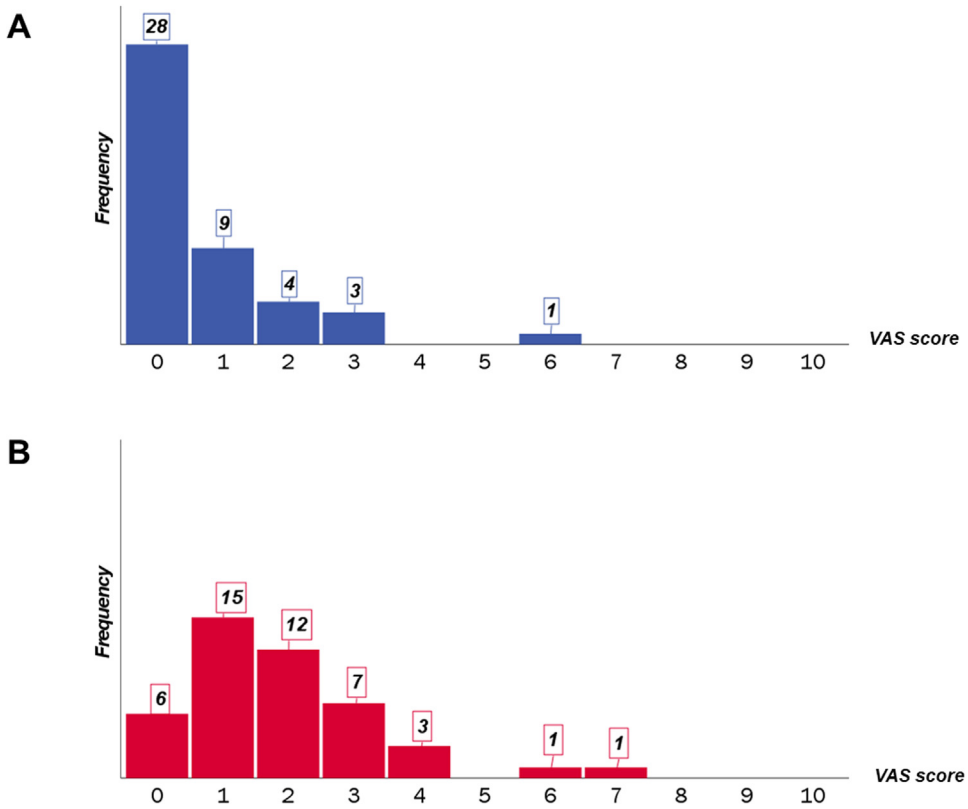

Fig. 2. Illustration of the primary outcome. Distribution of the overall intraoperative VAS score (primary outcome) of the ITM group (A) and the CON group (B). Abbreviations: control, CON; intrathecal morphine, ITM; visual analog scale, VAS.

the predefined opioid-related AEs occurred in the current study [19]. We found a greater percentage of patients subjected to ITM experienced pruritus, and further risk factor analyses suggested that patients with high BMI and smoking habit were more likely to experience pruritus after ITM. Besides, our results indicated that 100 μg ITM increased the risk of nausea or vomiting, but no significant difference was noticed. Although the study by Berger et al. [26] demonstrated that 50 μg ITM reduced the risk of pruritus compared with 100 μg ITM, the results from systematic reviews recommended the dose of 100 μg to balance the analgesia and harms of ITM [17,18]. Besides, it is worth mentioning that some AEs, including nausea, vomiting, hypertension and urinary retention, could be caused by ropivacaine itself [27]. Of note, prophylactic serotonin-receptor antagonists and opioid agonist-antagonists have been considered to be useful in preventing and relieving the side-effects of ITM [28,29].

Respiratory depression, the most feared adverse effect of opioids, has a particularly severe impact on PELD procedure which requires additional airway safety due to its prone position and no assisted ventilation. Respiratory depression following neuraxial morphine is categorize into early- (< 2 hours) and delayed-onset types (> 2 hours) [30]. Here, early-onset respiratory depression occurred in one 37-year-old healthy male patient treated with ITM, presenting with hypoxemia (<90%) and bradypnea (<10 breaths per minute) without any symptoms for more than 30 seconds at one hour postoperatively. The rescue remedy was supplemental oxygen via oxygen mask and 0.2 mg intravenous naloxone administered intravenously, and the patient's respiratory indicators successfully returned to normal after 15 minutes. The risk factors for opioid-induced respiratory

Table 2
Incidence of adverse events

	Patient group, No. (%)		
	ITM (n=43)	CON (N=45)	p value
Opioid-related AE			
Nausea or vomiting	13 (30)	7 (16)	.101*
Pruritus	8 (19)	1 (2)	.014*
Hypotension	2 (5)	1 (2)	.612*
Urinary retention	2 (5)	1 (2)	.612*
Respiratory depression	1 (2)	0 (0)	.489*
Anesthetic AE			
Shivering	4 (9)	1 (2)	.198*
Transient neurologic symptoms	7 (16)	7 (16)	.926*
Unexpected motor block	1 (2)	2 (4)	1.000*
Perianal numbness	2 (5)	2 (4)	1.000*
Surgical AE			
Rehospitalization	1 (2)	0 (0)	.489*
Reoperation	0 (0)	1 (2)	1.000*

Abbreviations: AE, adverse event; CON, control; ITM, intrathecal morphine.

* The Chi-square test or Fisher exact test.

depression include aging, female, co-existing morbidity, opioid-naïve patient, obesity, obstructive sleep apnea, but our study demonstrated that respiratory depression may still occur in healthy subjects [30]. Besides, although studies showed that respiratory depression was not observed in 50 to 200 μg ITM, these studies were ambiguous and inconsistent in the diagnosis of respiratory depression [18,26,31–34]. Additionally, Gonvers et al. [17] perfomed a systematic review on the application of ITM in joint surgery and concluded that 100 μg ITM warrants no more than standard postoperative care; however, we still recommended postoperative monitoring for the potential risk of respiratory depression of ITM based on our findings, unless future qualified evidence suggests otherwise.

Our study has several limitations. First, patients suitable for PELD were generally young, and we used a narrow eligibility criterion to ensure the participants' safety, and these factors limited the external validity of the results. Second, the sample size calculation was based on an independent t test of the primary outcome from the pilot study; however, the primary outcome was finally analyzed by nonparametric test, which may have affected the statistical power of the results. Our countermeasures were subgroup analyses and sensitivity analysis to verify the robustness of the primary outcome. Third, the data of level of block was not collected, and this may have led to bias in anesthesia evaluation. Lastly, despite the randomization, the baseline ODI score and herniated level were different between the two groups.

Conclusion

Our findings contributed to the current knowledge that adding 100 μg ITM to low-dose ropivacaine may be a good choice for PELD in terms of achieving adequate analgesia without motor impairment. However, 100 μg ITM increased the risk of pruritus and clinicians should be vigilant about potential risk of respiratory depression. Future studies are anticipated to identify if there is better ITM doses for PELD.

Acknowledgment

This study was supported by Interdisciplinary clinical research project of Peking University First Hospital (No. 2021CR31).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2023.03.001.

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