Liu et al. BMC Musculoskeletal Disorders (2024) 25:774
https://doi.org/10.1186/s12891-024-07898-w

BMC Musculoskeletal Disorders

RESEARCH

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# Comparison of spinal anesthesia and local anesthesia in percutaneous interlaminar endoscopic lumbar discectomy for L5/S1 disc herniation: a retrospective cohort study

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## Abstract

**Background** Interlaminar endoscopic lumbar discectomy (IELD) is a prevalent method for managing lumbar disc herniation. Local anesthesia (LA) is frequently employed during IELD, albeit with its merits and drawbacks. The spinal anesthesia (SA) represents a feasible anesthetic strategy for IELD; however, the availability of clinical research data is currently limited.

**Methods** The propensity score matching was conducted to ensure the comparability of the SA and LA groups. The outcome measures were operation time, intraoperative visual analogue scale (VAS) for pain, need for adjuvant analgesia, intraoperative vital signs, blood loss, adverse surgical events, anesthesia-related complications, postoperative bed rest duration, VAS for pain at 2 h postoperatively, Oswestry Disability Index score (ODI), satisfaction with surgical efficacy, and willingness to undergo reoperation at 6 months postoperatively.

**Results** Fifty-six patients were assigned to each group. Significant differences were found between the groups regarding intraoperative VAS for pain, use of adjuvant analgesics, willingness to undergo reoperation, maximum intraoperative systolic blood pressure, and variability ($P < 0.05$). Compared to the LA group, the SA group had lower VAS for pain at 2 h postoperatively, a longer operation time, a longer duration of postoperative bedrest, and more anesthesia-related complications ($P < 0.05$). No significant intergroup differences were detected in intraoperative heart rate variability, blood loss, ODI, satisfaction with surgical efficacy, and surgery-related complications ($P > 0.05$).

**Conclusion** SA as an alternative anesthesia for IELD surgery holds great promise, exhibiting superior efficacy compared to LA. However, it is crucial to meticulously evaluate the indications due to potential risks associated with this form of anesthesia.

**Keywords** Spinal anesthesia, Local anesthesia, Interlaminar endoscopic lumbar discectomy, IELD

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## Introduction

Lumbar intervertebral disc herniation is a prevalent spinal disorder in clinical practice, often accompanied by acute or chronic pain and symptoms of lower limb nerve compression, necessitating intervention for treatment [1]. The prevalence of lumbar disc herniation has been progressively increasing in recent years, posing significant challenges to healthcare and society while imposing substantial physical and economic burdens on patients [2].

Lumbar intervertebral disc herniation with failed conservative treatment is commonly treated with surgical intervention, which can relieve pain, restore function, and improve overall quality of life. Advances in spinal endoscopy have led to the widespread use of percutaneous endoscopic lumbar discectomy due to its benefits such as reduced invasiveness, faster recovery, minimal bleeding, and shorter hospital stay [3, 4]. Percutaneous endoscopic lumbar discectomy, encompassing transforaminal and interlaminar approaches, has gained widespread acceptance for treating lumbar disc herniation. Specifically, interlaminar endoscopic lumbar discectomy (IELD) is recommended for L5/S1 herniation due to unique anatomical characteristics such as the generous interlaminar space width and concealment of the L5/S1 foramen by the iliac crest [5, 6].

The anesthetic methods commonly used for IELD include general anesthesia and local anesthesia (LA) [7, 8]. LA enables direct patient communication and facilitates the assessment of nerve injury through feedback, such as lower limb activity, ensuring a high level of safety [9]. Additionally, LA has minimal impacts on respiratory and circulatory functions while promoting early mobilization, thus significantly reducing recovery time [10]. Therefore, LA has emerged as the predominant anesthesia method. However, intraoperative pain is frequently encountered during endoscopic discectomy under LA, particularly in the posterior interlaminar approach [11]. Consequently, certain patients may experience intolerable pain that necessitates suspension of the procedure. Furthermore, the experience of awake surgery may exacerbate patients' fear and anxiety, potentially impacting intraoperative hemodynamic stability. Therefore, it is not uncommon for IELD to be performed under general anesthesia, which offers the advantage of superior anesthetic efficacy. However, general anesthesia also brings more risks and complications, especially for older adults.

Spinal anesthesia (SA) can also be applied in IELD. SA in IELD reduces pain, shortens recovery time, and improves surgical conditions, enhancing overall efficacy and safety. Additionally, it lowers the risk of complications like infection and bleeding, reduces postoperative medication requirements, and decreases treatment costs. Overall, applying SA in IELD improves outcomes and enhances the surgical experience for patients and surgeons [12, 13].

The optimal anesthesia for IELD remains controversial. This retrospective propensity score-matched cohort study evaluated the anesthetic efficacy, surgical outcomes, and complications among patients who received SA or LA during IELD; the findings will provide valuable data to guide anesthesia selection.

## Methods

### Study design and patients

The study was approved by the Institutional Review Board of Ningbo No.6 Hospital (Ethical Review Board of Ningbo No.6 Hospital 2023 Paper No. 14) and adhered to the ethical principles outlined in the Declaration of Helsinki (revised in 2013). Informed consent was not required due to the retrospective design.

The cohort comprised patients who underwent initial L5/S1 unilateral IELD at Ningbo No.6 Hospital between February 1, 2021, and December 30, 2022. The inclusion criteria were: age 18–70 years, American Society of Anesthesiologists (ASA) grade I–II, and body mass index (BMI) 18–32 kg/m$^2$. The exclusion criteria were: general anesthesia, contraindications to intraspinal anesthesia administration, difficulty or failure of intraspinal puncture, and incomplete medical records.

### Data collection

The collected data were sex, age, ASA grade, BMI, operation time, intraoperative visual analogue score (VAS) for pain, need for additional analgesia, intraoperative changes in blood pressure and heart rate, blood loss, adverse events during surgery (dural sac tear, nerve root injury, vascular injury, hematoma formation, organ injury), complications associated with anesthesia (poisoning caused by anesthetic agents, cardiovascular incidents, urinary retention, other), duration of postoperative bedrest, VAS for pain at 2 h postoperatively, Oswestry Disability Index score (ODI), satisfaction with surgical efficacy, and satisfaction with surgery and anesthesia at 6 months postoperatively.

The intraoperative systolic blood pressure variability (SBPV) and heart rate variability (HRV) were used to characterize the fluctuations in intraoperative blood pressure and heart rate. SBPV was calculated as the difference between the maximum and minimum blood pressure values divided by the minimum blood pressure, while HRV was calculated by dividing the difference between the maximum and minimum heart rate values by the minimum heart rate. Monitoring these two variables intraoperatively gives clinicians a better understanding of how well a patient is tolerating anesthesia and helps identify patients at higher risk of postoperative complications such as stroke or cardiac events. Overall, evaluating the SBPV and HRV is essential in ensuring safe surgical outcomes. The operating surgeon initially estimates blood loss based on endoscopic observations, which are subsequently validated by the anesthesiologist and circulating nurse through precise inflow and outflow measurements during the irrigation process.

The ODI was employed to assess the therapeutic outcome of the patient's disability severity at 6 months following surgery. The ODI was calculated using a questionnaire comprising ten scored questions on pain, sensation, function, and impact on daily life; the maximum total cumulative score was 50 points, with a higher ODI indicating worse functionality. The modified MacNab standard was used to assess the surgical efficacy at 6 months postoperatively as 3 (excellent; complete disappearance of symptoms with full restoration of original work and daily activities), 2 (good; mild symptoms with slight activity limitation but no impact on work and life), 1 (fair; alleviation of symptoms with limited activity affecting normal work and life), or 0 (poor; no improvement or even worsening compared with the pre-treatment condition) [14]. The Likert scale was used to assess the patients' perception of their surgical and anesthetic experience at 6 months postoperatively as 0 (extremely unsatisfied), 1 (unsatisfied), 2 (moderate), 3 (satisfied), or 4 (highly satisfied); this was the score was used to indicate the patients willingness to undergo reoperation.

### Anesthesia

Experienced anesthesiologists and surgeons performed the anesthesia and surgery for all patients in this study.

(1) The LA group received 1% lidocaine infiltration around the skin puncture site, deep fascia, articular process, and ligamentum flavum. Throughout surgery, a dedicated anesthesiologist closely monitored the patients' lower limb sensations. The patient was in the prone position with the head supported and soft pillows placed at the armpit and waist levels. A cushion was securely fastened between the two lower limbs, while a belt was firmly secured to ensure trunk stability. The C-arm X-ray machine was used to precisely mark the surgical segment and puncture site.

(2) In the SA group, the patient was positioned laterally with electrocardiogram monitoring, and the body was flexed to optimize lumbar intervertebral space exposure. Subsequently, the L3/4 intervertebral space was identified, followed by gradual infiltration of 1% lidocaine at the puncture site. A median approach was used for needle insertion into the subarachnoid space. Needle advancement was ceased upon visualization of cerebrospinal fluid outflow. To ensure an aseptic technique, 2.0 ml of 0.5% ropivacaine was administered without any blood withdrawal. Following completion of the injection, the patient remained in a supine position under close observation for 15 min before transitioning to the appropriate surgical position once the anesthesia reached a stable plane.

### Operation

The patient was positioned in the prone position on a specialized surgical bed. Before the procedure, the C-arm machine precisely localized the needle insertion point. Under X-ray fluoroscopic guidance, a 23-gauge guide pin was inserted close to the outer boundary of the interlaminar window. Subsequently, a 0.8-mm-diameter guidewire replaced the needle, and an expander was bluntly inserted to open the paravertebral muscle and establish a working channel. Fluoroscopy confirmed that the working channel was positioned towards the lateral margin of the interlaminar fenestration. A spinal endoscope (Joimax Inc., Irvine, California, USA) was introduced. The ligamentum flavum was incised from its junction with the facet joint to expose the lateral edge of the nerve root for direct visualization and removal of herniated discs. Following successful decompression of the nerve root and achievement of hemostasis, both the endoscope and working tube were safely withdrawn.

### Statistical analysis

The propensity scores of the two groups were matched using SPSS software (version 24.0). Propensity scores for each patient were estimated using the anesthesia method as the grouping variable, and age, sex, BMI, ASA grade, and preoperative VAS for pain as predictive variables. Matching was performed in a 1:1 ratio with a matching tolerance of 0.1. Subsequently, the balance of matching was assessed. Statistical analysis was conducted using SPSS software (version 24.0). Firstly, the normality of the data was assessed using the Kolmogorov-Smirnov test. Quantitative data that followed a normal distribution were presented as mean ± SD and compared using an independent samples t-test. Additionally, the Welch test was employed to examine variance differences between the two groups, and in cases of unequal variances, results were adjusted using the Welch-t test. For non-normally distributed qualitative data, median (lower quartile, upper quartile) values were reported and group differences were evaluated using the Mann-Whitney test. Categorical data were described as counts and analyzed using the chi-squared test. $P < 0.05$ denoted statistical significance.

## Results

A total of 236 patients underwent unilateral L5/S1 IELD surgery at Ningbo No.6 Hospital between February 1, 2021, and December 30, 2022, as identified through a retrospective search. Following screening, inclusion criteria were met by 115 patients comprising 56 with LA and 59 with SA. After matching based on sex, age, BMI,

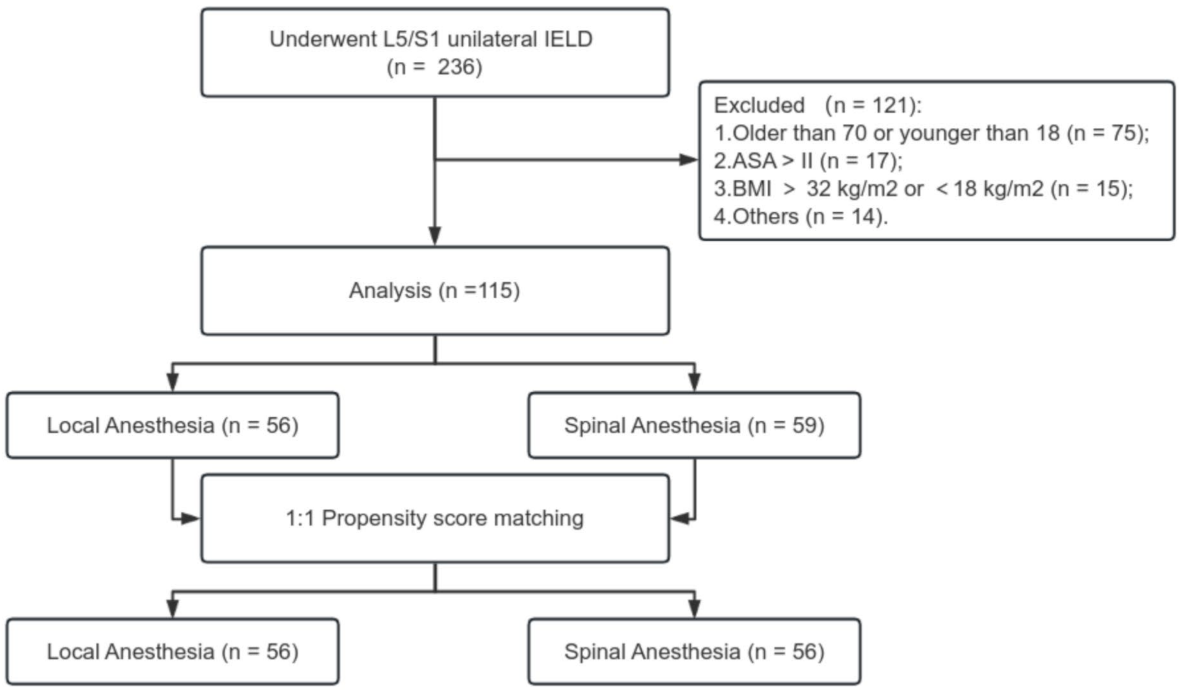


**Fig. 1** Flow chart

**Table 1** Comparative analysis of general conditions observed in the two groups

| | Unmatched | | | Matched | | |
|---|---|---|---|---|---|---|
| **Characteristics** | **LA** | **SA** | ***P*** | **LA** | **SA** | ***P*** |
| Number | 56 | 59 | | 56 | 56 | |
| Age, year | 44.1 ± 14.1 | 41.4 ± 11.2 | 0.245 | 44.1 ± 14.1 | 41.0 ± 10.9 | 0.187[&] |
| Gender (male/female) | 34 / 22 | 36 / 23 | 0.973 | 34 / 22 | 35 / 21 | 0.846 |
| BMI, kg/m$^2$ | 24.6 ± 3.2 | 23.7 ± 2.9 | 0.111 | 24.6 ± 3.2 | 23.9 ± 2.8 | 0.173 |
| ASA grade (I / II) | 13 / 43 | 14 / 45 | 0.948 | 13 / 43 | 13 / 43 | 1.000 |
| Preoperative VAS | 7.1 ± 1.3 | 7.0 ± 1.4 | 0.724 | 7.1 ± 1.3 | 7.0 ± 1.4 | 0.620 |

[&] The Welch-t-test was employed to compare differences between groups when the variances were unequal. LA: local anesthesia, SA: Spinal anesthesia, BMI: Body Mass Index, ASA: American Society of Anesthesiologists, VAS: Visual Analogue Score

**Table 2** Comparison of intraoperative observation indexes after matching propensity score

| **Characteristics** | **LA** | **SA** | ***P*** |
|---|---|---|---|
| Intraoperative VAS | 2.3 ± 1.2 | 0.2 ± 0.7 | <0.001[&] |
| Analgesic drugs (yes / no) | 11 / 45 | 2 / 54 | 0.008 |
| Intraoperative Max-SBP | 148.5 ± 17.7 | 138.5 ± 13.0 | 0.001[&] |
| Intraoperative SBPV, % | 24.2 ± 14.4 | 18.6 ± 9.4 | 0.016[&] |
| Intraoperative HRV, % | 28.5 (18.1, 34.4) | 27.3 (20.9, 38.3) | 0.511 |
| Blood loss, ml | 10 (10, 20) | 20 (10, 20) | 0.797 |
| Operation time, min | 60.0 (50.0, 70.0) | 70.0 (55.0, 83.8) | 0.006 |

[&] The Welch-t-test was employed to compare differences between groups when the variances were unequal. LA: local anesthesia, SA: Spinal anesthesia, VAS: Visual Analogue Score, SBPV: systolic blood pressure variability, HRV: heart rate variability

ASA grade, and preoperative VAS for pain with a ratio of 1:1 between the LA and SA groups, the cohort ultimately comprised 56 patients who received LA and 56 who underwent SA (Fig. 1). After matching, there were no significant differences between the LA and SA groups in age, sex, BMI, ASA grade, and preoperative VAS for pain (Table 1).

Spinal anesthesia provided superior intraoperative analgesia and more stable hemodynamics (Table 2). The intraoperative VAS for pain, use of adjuvant analgesics, maximum intraoperative systolic blood pressure, and intraoperative SBPV exhibited significant differences between the two groups ($P<0.05$). There were no significant differences between groups in the intraoperative HRV and blood loss ($P>0.05$). However, the SA group had a longer operation time than the LA group ($P<0.05$).

**Table 3** Comparison of postoperative observation indexes after matching propensity score

| Characteristics | LA | SA | *P* |
| --- | --- | --- | --- |
| Postoperative VAS * | 2(2,3) | 2(1,2) | 0.019 |
| Bed rest time, min | 94.6±21.9 | 248.4±39.3 | <0.001 & |
| Complications associated with anesthesia (yes / no) # | 0 / 56 | 4 / 52 | 0.042 |
| Adverse events during surgery (yes / no) | 1 /55 | 0 / 56 | 0.315 |

* Reassessment conducted 2 h post-surgical procedure. # The potential complications encompass urinary retention, nausea, vomiting, and headache, among others. & The Welch-t-test was employed to compare differences between groups when the variances were unequal. LA: local anesthesia, SA: Spinal anesthesia, VAS: Visual Analogue Score

**Table 4** Follow-up and evaluation at six months after operation

| Characteristics | LA | SA | *P* |
| --- | --- | --- | --- |
| ODI | 7.4±2.9 | 7.3±2.9 | 0.845 |
| Satisfaction with surgical efficacy | | | |
| excellent | 6 | 3 | 0.286 |
| good | 29 | 27 | |
| fair | 20 | 26 | |
| poor | 1 | 0 | |
| Satisfaction with surgery and anesthesia | | | |
| extremely unsatisfied | 0 | 0 | <0.001 |
| unsatisfied | 10 | 1 | |
| moderate | 25 | 9 | |
| satisfied | 19 | 31 | |
| highly satisfied | 2 | 15 | |

LA: local anesthesia, SA: Spinal anesthesia, ODI: Oswestry Disability Index

The postoperative follow-up outcomes of the two groups are presented in Table 3. The VAS for pain at 2 h postoperatively was significantly lower in the SA group than in the LA group ($P<0.05$). Additionally, the SA group had a significantly longer duration of postoperative bed rest than the LA group ($P<0.05$). In the SA group, two patients experienced transient urinary retention, one reported a mild headache, and another had postoperative nausea. In the LA group, one patient encountered dizziness and nausea; however, due to the inability to establish causality with anesthesia, it was excluded from the statistical analysis. There were more anesthesia-related complications in the SA group than in the LA group ($P<0.05$), both groups had similarly low incidences of surgery-related complications ($P>0.05$).

The two groups were followed up for 6 months (Table 4). Comparative analysis revealed no significant differences between the two groups in the ODI and satisfaction with surgical efficacy ($P>0.05$). The satisfaction with surgery and anesthesia in the SA group was significantly higher compared to that in the LA group ($P<0.05$).

## Discussions

This retrospective propensity score-matched cohort study revealed significant differences between the LA and SA groups in the intraoperative VAS for pain, use of intravenous adjunctive analgesics, maximum intraoperative systolic blood pressure, intraoperative SBPV, 2-hour postoperative VAS for pain, postoperative bed rest duration, and anesthesia-related complications among patients undergoing L5/S1 unilateral IELD. SA provided superior intraoperative and early postoperative (within 2 h) analgesia as well as more stable blood pressure; however, it was associated with increased operation time, postoperative bed rest duration, and anesthesia-related complications such as urinary retention. There were no significant differences between the LA and SA groups regarding intraoperative HRV, blood loss volume, ODI at 6 months postoperatively, or patient-rated satisfaction with the surgical efficacy. However, the SA group reported higher levels of postoperative satisfaction than the LA group.

Anesthesia is a pharmacological intervention used to mitigate pain and induce unconsciousness during surgical interventions [15]. The forms of anesthesia include LA, regional anesthesia, and general anesthesia [16]. LA selectively desensitizes a specific region of the body, regional anesthesia blocks nerve conduction in larger areas such as limbs [17, 18], and general anesthesia induces profound sedation, rendering patients insensible to surgical stimuli [19]. The advent of anesthesia has revolutionized surgery by facilitating procedures that would otherwise be intolerably painful. The essence of anesthesia is to provide analgesia and comfort during surgical interventions, thereby promoting swifter recuperation with fewer complications [20, 21].

The present study found that SA had a better intraoperative analgesic effect than LA, which was consistent with the expected results. SA is widely used in clinical practice and involves the precise administration of local anesthetics into the subarachnoid space to target the corresponding spinal nerve [22–24]; this skill represents one of the fundamental proficiencies mastered by anesthesiologists. The direct blockade of the nerve root by local anesthetics enables a profound anesthetic effect, with the efficacy contingent upon the extent of the block. Therefore, the SA group had a significantly greater level of satisfaction with the anesthesia than the LA group.

The fluctuation of blood pressure in patients receiving SA is reduced due to the attenuation of intraoperative surgical stimulation, thereby mitigating the stress response induced by pain. Hypotension is a common side effect of SA spinal anesthesia, resulting from the blockade of the sympathetic nervous system. Careful selection of local anesthetic dose is crucial to prevent circulatory inhibition due to a high anesthetic level [23]. No instances of post-anesthesia hypotension were observed in this study; however, it is important to acknowledge that individual patients may exhibit varying hemodynamic responses to spinal anesthesia. Factors such as patient age, underlying cardiovascular conditions, specific surgical procedures, and other variables can influence the stability of hemodynamics during surgery. Therefore, when selecting an appropriate anesthesia approach, multiple factors should be taken into consideration. Simultaneously, timely fluid supplementation must be administered to maintain a balanced distribution of blood volume [25].

The present study revealed no significant differences between the LA and SA groups in the surgical outcomes and incidence of surgery-related complications, thereby demonstrating that the anesthesia method had minimal influence on the surgical efficacy. SA attenuates nerve sensation in the lower limbs without increasing the likelihood of intraoperative nerve injury under skilled surgical management [12]. Throughout the study, no evidence of CSF leak was observed under the endoscope. Furthermore, there were no complications associated with CSF leaks in patients undergoing SA. Previous research has demonstrated that the incidence of CSF leak with a 27 G needle during spinal anesthesia is extremely low [26]. It is important to avoid repeated punctures.

The results of this study demonstrated a significant disparity in the duration of surgery between the two anesthesia techniques. It is worth noting that previous related studies have also reported diverse outcomes in operation time [5, 6]. The limited sample size employed in these studies may account for the observed statistical differences. Furthermore, the operation time of both groups in this study fell within the average range documented by other investigations, indicating normalcy. Additionally, it is imperative to acknowledge that various factors such as surgeon expertise and patient individuality can influence operative duration. This study found that the difference between the two groups of operation time is only 10 min or less. Despite the lack of direct evidence, we are more inclined to believe that this difference has no practical clinical significance.

The most significant advantage of LA is that the patient's lower limb sensation and movement are retained intraoperatively, which enables the timely detection of nerve traction or injury [9, 27]. However, the effect of LA varies with the level at which the anesthetic agent is injected. In clinical practice, there are often cases with poor effects of LA. We believe that the choice of anesthesia should consider the patients' experience in addition to considering the requirements of surgery to ensure safety.

The findings of this study suggest that compared to local anesthesia (LA), spinal anesthesia (SA) may be associated with a higher incidence of anesthesia-related complications and prolonged postoperative bed rest time. In the SA group, two patients experienced transient urinary retention, one reported a mild headache, and another had postoperative nausea. It is important to note that no severe consequences were observed in the reported cases. These manifestations are inherent to SA [24, 28–31]. Timely and appropriate symptomatic treatment is particularly important. Patients should be closely observed postoperatively, especially patients with certain diseases such as benign prostatic hyperplasia or hypercoagulability. However, it is important to acknowledge that postoperative patients following LA are not exempt from the potential occurrence of headache, nausea, and vomiting; in fact, these symptoms may even be more prevalent. This could potentially be attributed to suboptimal anesthetic efficacy, heightened stress response, and/or increased demand for intravenous analgesics. While these manifestations cannot be classified as complications directly related to anesthesia administration, they should not be disregarded.

To enhance patient comfort, general anesthesia is commonly used for surgery [7, 8, 32]. General anesthesia is the administration of anesthetic agents that induce a state of unconsciousness [33]. The advantages of general anesthesia include effective management of discomfort during surgical procedures, facilitation of muscle relaxation, and assurance of patient immobility. However, general anesthesia is not devoid of risks. Particularly in older adults with underlying health conditions, general anesthesia may increase the likelihood of cardiovascular and cerebral incidents due to varying effects on the cardiovascular system [34, 35].

Epidural anesthesia has been used in IELD, with good effectiveness and safety [32, 36]. Epidural anesthesia reduces pain and anxiety, minimizes the risks of respiratory and cardiovascular complications, and allows for a more comfortable and relaxed surgical experience for the patient, which can contribute to faster recovery and better overall outcomes [32, 36]. The advantage of epidural anesthesia for IELD lies in its ability to preserve partial lower limb sensation similar to LA, enabling accurate feedback on nerve traction while providing superior analgesic effects [32]. However, epidural anesthesia entails greater puncture trauma than SA, and the continuous epidural block may pose increased risks of infection, hematoma formation, and nerve injury [37, 38].

Ultimately, the selection of anesthesia must involve a comprehensive preoperative assessment and detailed patient education [39]. To minimize adverse consequences, it is advisable to limit the use of spinal anesthesia in cases involving bleeding tendency, spinal anatomical variation, circulatory failure, and infection. Furthermore, patients at high risk of lower extremity thrombosis or experiencing dysuria should avoid spinal anesthesia. Conversely, when patients exhibit anxiety, hyperalgesia or hypertension, the benefits of spinal anesthesia are enhanced due to its superior analgesic efficacy. By fully considering patients' preferences and circumstances, anesthesiologists can create optimal personalized anesthesia protocols.

## Conclusion

The findings of this study suggest that SA may serve as a promising alternative anesthesia for IELD surgery. Compared to LA, SA can achieve superior anesthetic efficacy. Nevertheless, it is crucial not to overlook the potential risks associated with anesthesia, necessitating a meticulous evaluation of indications.

**Acknowledgements**
We thank Kelly Zammit, BVSc, from Liwen Bianji (Edanz) (www.liwenbianji.cn/), for editing the English text of a draft of this manuscript.

**Author contributions**
All authors contributed to the study conception and design. The surgical procedure and administration of anesthesia were conducted by Guanyi Liu, Long Zhang, and Liyong Yuan. Material preparation, data collection and analysis were performed by Jiawei Zhang, Long Zhang, Xuan Wang and Dilraba Tursunmamat. The first draft of the manuscript was written by Guanyi Liu and Long Zhang， and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Funding**
This study was financially supported by the Ningbo Public Welfare Research Plan Key Project (No. 2023S036), Ningbo "Science and Technology Yongjiang 2035" Science and Technology Innovation Ecological Incubation Plan (No.: 2024Z048), and Science and Technology Project for Agricultural and Social Development in Yinzhou District (No. 2024AS036).

**Data availability**
The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

**Code availability**
Not applicable.

## Declarations

**Ethics approval and consent to participate**
This study was performed in line with the principles of the Declaration of Helsinki. The present study was conducted retrospectively and received approval from the Ethics Committee of Ningbo Sixth Hospital, with all patients providing informed consent for the utilization of their medical records.

**Conflict of interest**
The authors declare no conflict of interest.

**Consent for publication**
Not Applicable.

**Competing interests**
The authors declare no competing interests.

Received: 4 January 2024 / Accepted: 23 September 2024
Published online: 02 October 2024

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