Randomized Trial

Quantitative Evaluation of the Trauma of CT Navigation PELD and OD in the Treatment of HLDH: A Randomized, Controlled Study

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Background: More evidence is required to support that computerized tomography navigation percutaneous spinal endoscopy in the treatment of highly migrated lumbar disc herniation is a more minimally invasive surgery than open discectomy .

Objective: To quantitatively evaluate the efficacy and minimal invasiveness of computerized tomography navigation percutaneous spinal endoscopy and open discectomy in highly migrated lumbar disc herniation.

Study Design: A prospective randomized study.

Setting: First Affiliated Hospital of Gannan Medical College.

Methods: From August 2016 to February 2020, 68 patients with highly migrated lumbar disc herniation had undergone discectomy. Thirty-five of them randomly received computerized tomography (CT) navigation percutaneous spinal endoscopy at the pain department (CT navigation percutaneous spinal endoscopy group), and 33 patients received open discectomy at the orthopedics department (open discectomy group). The Visual Analog Scale (VAS) score, Japanese Orthopaedic Association (JOA) score, and modified MacNab criteria were applied to evaluate the clinical situations pre- and post-operation. The serum concentrations of IL-6, TNF-α, creatine phosphokina (CPK), and C-reactive protein (CRP) in the 2 groups were quantitatively measured.

Results: The postoperative VAS scores of the back and lower extremity were lower than those pre-operation in both groups, while the VAS score of back pain in the open discectomy group was significantly higher than that in the CT navigation percutaneous spinal endoscopy group at one week post-operation ($P < 0.01$). The postoperative JOA scores were significantly higher than those pre-operation in both groups. The serum concentrations of IL-6, TNF-α, CPK, and CRP in the open discectomy group were higher than those in the computerized tomography navigation percutaneous spinal endoscopy group postoperatively ($P < 0.01$).

Limitations: This is a single-center randomized study and with the limitation of the sample size.

Conclusion: CT navigation percutaneous spinal endoscopy is a more minimally invasive surgery than open discectomy.

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Key words: Highly migrated lumbar disc herniation, endoscopic, CT navigation, trauma

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Lumbar disc herniations (LDHs) frequently cause lower back pain and sciatica. Approximately 70% – 85% of the general population have at least one episode of lower back pain with or without leg pain during their lives (1-3). LDH is a relevant health problem that affects one's quality of life, resulting in high health costs and economic loss worldwide (4). Generally, surgical treatment is necessary when conservative treatment fails.

Percutaneous endoscopic lumbar discectomy (PELD) is a minimally invasive surgery for LDH and is an alternative to conventional open surgery for LDH (5-7). The PELD technique can achieve clinical outcomes comparable to those of conventional open surgery (5,7). However, highly migrated lumbar disc herniation (HLDH) due to herniated lesions results in a further shift of the lumbar disc and anatomical obstruction of the facet joints, pedicle, and posterior margin of the vertebral body. Certain questions must be considered when performing PELD. The computed tomography (CT) intraoperative navigation technique, which combines preoperative and intermittent intraoperative CT, has been described as an advanced minimally invasive technique. Relative to two-dimensional (2-D) fluoroscopy, this technique offers superior radiologic anatomic resolution, a reduced incision length, and decreased radiation exposure to surgeons and operating room (OR) staff (8). Currently, CT-navigation PELD (CT-PELD) for highly migrated lumbar disc herniation (HLDH) has not been clearly described.

This study aimed to (1) quantitatively compare the traumatic and inflammatory effects and clinical outcomes between CT-PELD and traditional open discectomy (OD) and (2) evaluate how the clinical advantages of CT-PELD are mirrored in an improved biochemical inflammatory and traumatic biomarker profile.

Methods

General Information

A randomized clinical trial was conducted to compare 2 surgical approaches with the treatment of HLDHs that are refractory to clinical treatment. Patients diagnosed with HLDH were randomly recruited to the pain or spine department of a public university hospital: those treated at the pain department were assigned to the PELD group and those treated at the spine department were assigned to the OD group. The outpatients in the 2 departments were comparable. All the patients signed informed consent forms. The study protocol was approved by the local ethics committee and is registered in a clinical trials registration database (LLSC-2021062201).

Thirty-five patients who had lower back and leg pain due to HLDH had undergone PELD at the pain department, and 33 patients had undergone OD at the spine department between December 2016 and January 2020. The basic demographic and clinical characteristics of the patients, including age, gender, disease course, follow-up time, location of lesions, and intraoperative duration, were collected (Table 1). Routine magnetic resonance imaging (MRI) scans were conducted to confirm the level of the lesions and classification of the herniated discs (9) before surgery (Table 2). The inclusion and exclusion criteria are presented in Table 3. All the patients were followed by telephone or an outpatient recheck.

CT-PELD

Patients were administered local anesthesia before surgery. Two possible endoscopic approaches for direct HLDH decompression were used: the classic transforaminal (TF) approach and interlaminar (IL) approach. The choice for IL or TF in this study depended on the position of the protrusion, nerve root, dural sac, CT image obtained during the operation, and surgeon's preference for each case. The precise target of puncture and location of the dilator and work tube were guided by CT in a timely manner during surgery. Standard endoscopic surgery (IL or TF) was conducted as described in a previous study (10).

OD

Patients in the OD group were administered general anesthesia. Patients were taken to the operating table, where, in the prone position, the herniation level was determined using fluoroscopy, and the lamina and interlaminar spaces of the related herniation were exposed. Next, an incision was made at the midline of the median skin and fascia, and the paravertebral tissues were retracted. From this stage, using a curette, the ligamentum flavum was retracted and dropped from the insertion point to the lamina, the spinal cord and nerve roots were observed after partial laminectomy and removal of the ligamentum flavum, and the nerve root was made completely visible after opening the foramen. After gentle medial retraction using a nerve hook, the disc material was removed, the posterior longitudinal ligament was opened, and the degenerative disc contents were removed. After checking the epidural space, the layers were appropriately closed.

Table 1. *Demographic and clinical characteristics.*

Parameters	CT - PELD	OD	*P* value
Age (year)	48.7 ± 10.1 (24 - 70)	46.6 ± 10.2 (22 - 69)	0.41
Gender			
Male	24	18	0.32
Female	11	15	
Course of disease (month)	3.2 ± 8.2 (0.1 - 48)	3.6 ± 3.4 (0.1 - 12)	0.79
Intraoperative duration (minute)	97.6 ± 38.2 (60 - 150)	80.3 ± 22.4 (60 - 100)	< 0.0001
Follow-up time (month)	17.2 ± 13.5 (6 - 46)	16.6 ± 5.8 (6 - 25)	0.83
Location of lesions			
L2/3	1	1	0.25
L3/4	4	0	
L4/5	17	17	
L5/S1	13	15	
Surgery approach			
Interlaminar approach	21 (L3/4:1, L4/5:9, L5/S1:11)	33	
Foramen approach	14 (L3/4:3, L4/5:8, L5/S1:2)	0	

Table 2. *Classification of Migrated Disc Herniations (9).*

(1) High-cranial migration	From the inferior margin of the upper pedicle to 3 mm below the inferior margin of the upper pedicle.
(2) Near-cranial migration	From 3 mm below the inferior margin of the upper pedicle to the inferior margin of the upper vertebral body.
(3) Near-caudal migration	From the superior margin of the lower vertebral body to the center of the lower pedicle.
(4) High-caudal migration	From the center to the inferior margin of the lower pedicle.

Table 3. *Inclusion and Exclusion Criteria.*

Inclusion Criteria	
1	Complaining of low back and lower limb pain or numbness due to highly prolapsed lumbar disc herniations (23).
2	Positive straight leg raising test (< 60°) and positive augmentation test.
3	Unsuccessful conservative treatment for more than 3 months or with obvious sciatic and femoral nerves damage.
Exclusion Criteria	
1	Severe disc calcification confirmed by CT.
2	Recurrent disc herniations after open discectomy or PELD.
3	Combined with spine instability.
4	With rheumatal-immune-related diseases or long-term use of glucocorticoid drugs.
5	Infection or clinical symptoms caused by multilevel disc herniations.

Clinical Assessments

The clinical data were collected pre-operation and at postoperative one week, one month, 3 months, 6 months, 12 months, and the last follow-up. Back pain and leg pain were measured using the Visual Analog Scale (VAS), with scores ranging from 0 points (no pain) to 10 points (worst pain). The neurofunctional state was assessed using the Japanese Orthopaedic Association (JOA) score. The intraoperative duration and complications were also documented and analyzed. The satisfaction rate of the clinical outcomes was assessed according to the modified MacNab criteria (11).

Blood Sampling and Analysis

Venous blood was collected on day 2 of admission (pre-operation), immediately post-operation, 48 hours post-operation, and one week post-operation. Blood was collected between 6:00 AM and 7:00 AM each day to reduce variability resulting from diurnal variations. Cytokine concentrations and trauma markers in the serum were analyzed. One 5-mL blood sample was drawn into glass tubes containing 35 μmol of dipotassium ethylenediaminetetraacetic acid and 1,500 kallikrein inactivator units of Trasylol. The tubes were kept in an ice bath and then centrifuged at 2,000×g for 15 minutes at 4°C. Plasma was separated from the cells, stored at -80°C, and analyzed using a commercially available enzyme-linked immunosorbent assay (ELISA) kit.

ELISA

The protein levels of the inflammatory cytokines TNF-α and IL-6 and the trauma indicators creatine phosphokinase (CPK) and C-reactive protein (CRP) were determined from the sera of patients in the 2 groups pre- and post-operation. Commercial ELISA kits were used in accordance with the manufacturer's instructions (R&D Systems, Inc., USA). The assays were performed in duplicate in 96-well plates. The collected samples were analyzed on the same day on one ELISA plate for each biomarker.

Statistical Analysis

The Kolmogorov-Smirnov test was used to test the normality of all the variables. Between-group differences were compared using Student's t-test for continuous

variables (mean ± standard deviation [SD]) or chi-squared test for categorical variables (n [%]). Differences in the longitudinal changes in the VAS and JOA scores between the CT-PELD and OD groups were compared using repeated measures analysis of variance. All the analyses were performed using SPSS version 20.0 (SPSS Inc., Chicago, IL) and Prism 8 Software (La Jolla, CA). *P* values less than 0.05 were considered statistically significant.

Results

Clinical Results

Sixty-eight patients were enrolled in our study: 35 in the CT-PELD group (men: 24; women: 11; average age: 48.7 ± 10.1 [24 – 70] years) and 33 in the OD group (men: 18; women 15; average age: 46.6 ± 10.2 [22 – 69] years). No significant differences were found in age or gender between the 2 groups. The average course of disease (3.2 ± 8.2 [0.1 – 48] months versus 3.6 ± 3.4 [0.1 – 12] months, $P = 0.79$) and follow-up time (17.2 ± 13.5 [6 – 46] months versus 16.6 ± 5.8 [6 – 25] months, $P = 0.83$) were comparable between the CT-PELD and OD groups. However, the average intraoperative duration of the CT-PELD group was relatively longer than that of the OD group (97.6 ± 38.2 [60 – 150] min versus 80.3 ± 22.4 [60 – 100] min, $P < 0.01$). Additionally, the locations of lesions in the CT-PELD group were L2/3 (n = 1), L3/4 (n = 4), L4/5 (n = 17), and L5/S1 (n = 13), which were similar to those in the OD group (L2/3 [n = 1], L4/5 [n = 17], and L5/S1 [n = 5]). Two patients in the CT-PELD group were lost to follow-up, and no patient in the OD group was lost to follow-up. The demographic and clinical characteristics are presented in Table 1.

We compared the back VAS (B-VAS) and leg VAS (L-VAS) scores between the CT-PELD and OD groups pre-operation and at post-operative one week, one month, 3 months, 6 months, 12 months, and at the final follow-up and compared the lumbar JOA scores before surgery, at post-operative one week, one month, 6 months, 12 months, and at the final follow-up (Table 4, Fig. 1). The VAS scores of the back and leg significantly were decreased across the postoperative interviews after treatment with CT-PELD ($P < 0.01$) and OD ($P < 0.01$). However, the B-VAS was higher in the OD group one week postoperatively. The JOA scores also improved from pre-operation to the final follow-up in the CT-PELD group (3.8 ± 2.8 to 28.4 ± 0.6) ($P < 0.01$) and in the OD group (3.9 ± 3.6 to 27.3 ± 2.0) ($P < 0.01$). No significant differences were found in the lumbar JOA score between the 2 groups after surgery (Table 4).

Next, we evaluated the satisfaction rate of the clinical outcomes at the final follow-up according to the modified MacNab criteria. In the CT-PELD group, the outcomes of 27 patients were excellent and 6 were good; in the OD group, the outcomes of 23 patients were excellent, 9 were good, and one was fair (Table 4). No significant differences were found in the satisfaction rates (excellent and good) between these 2 surgical procedures (100% versus 97%; $P = 0.38$).

The current findings suggested that the migrated disc was successfully removed and confirmed by MRI examinations post-operation (Figs. 2 and 3). No complications were reported during the operation in the 2 groups. In the OD group, one patient developed surgical incision infection 4 days postoperatively, and one patient experienced cauda equina injury persistently with numbness in the saddle area 13 months after surgery. In the CT-PELD group, one patient showed recurrence 2 years post-operation and received secondary surgery.

Serum Results

In the CT-PELD group, the serum concentrations of IL-6 showed different levels: they decreased immediately post-operation and 48 hours and one week post-operation. The lowest value was observed at 48 hours post-operation, which was significantly lower than that pre-operation ($P < 0.01$). However, in the OD group, the serum concentrations of IL-6 were significantly elevated immediately post-operation and 48 hours and one week post-operation ($P < 0.01$), and the highest value was observed at 48 hours post-operation ($P < 0.01$) (Fig. 4). The serum concentrations of IL-6 were higher in the OD group than in the CT-PELD group immediately, 48 hours, and one week post-operation ($P < 0.01$) (Fig. 4).

The serum concentrations of TNF-α were decreased in both groups immediately after surgery, but they were significantly lower in the CT-PELD group than in the OD group. However, in the OD group, the concentrations increased at 48 hours and one week after surgery, and the highest value was observed at one week after surgery, significantly higher than the preoperative value. In the CT-PELD group, no increasing tendency of TNF-α was found at 48 hours and one week after surgery (Fig. 4).

In the CT-PELD group, the serum concentrations of CPK were significantly decreased at 48 hours and one week after surgery; by contrast, in the OD group, the concentrations were increased immediately and 48 hours after surgery and then were decreased one week after surgery ($P < 0.01$; Fig. 5). No difference was found

Table 4. *Clinical outcomes and complications of 2 groups (n = 66).*

Parameters	CT - PELD	OD	*P* value
VAS score of leg			
Pre-operation	7.48 ± 1.03	7.47 ± 1.11	> 0.99
After 1 week	1.30 ± 1.07	2.44 ± 0.72	< 0.01
After 1 month	0.97 ± 0.88	1.19 ± 0.82	0.25
After 3 months	0.67 ± 0.82	0.91 ± 0.93	0.21
After 6 months	0.55 ± 0.71	0.84 ± 0.92	0.11
After 12 months	0.58 ± 0.90	0.75 ± 0.84	0.58
Last follow-up	0.58 ± 0.71	0.81 ± 0.83	0.24
JOA score			
Pre-operation	3.79 ± 0.79	3.91 ± 3.64	0.883302
After 1 week	21.06 ± 2.83	20.50 ± 3.33	0.466719
After 3 months	24.64 ± 1.45	25.88 ± 2.04	0.006372
After 6 months	27.30 ± 1.23	27.06 ± 2.05	0.567064
After 12 months	28.36 ± 0.67	27.21 ± 2.13	0.089886
Last follow-up	28.40 ± 0.65	27.53 ± 0.77	0.023400
Modified MacNab criteria			
Excellent	27	23	0.38
Good	6	9	
Fair	0	1	
Poor	0	0	
Complications			
Infection	0	1 (33)	> 0.99
Recurrence	1 (33)	0	

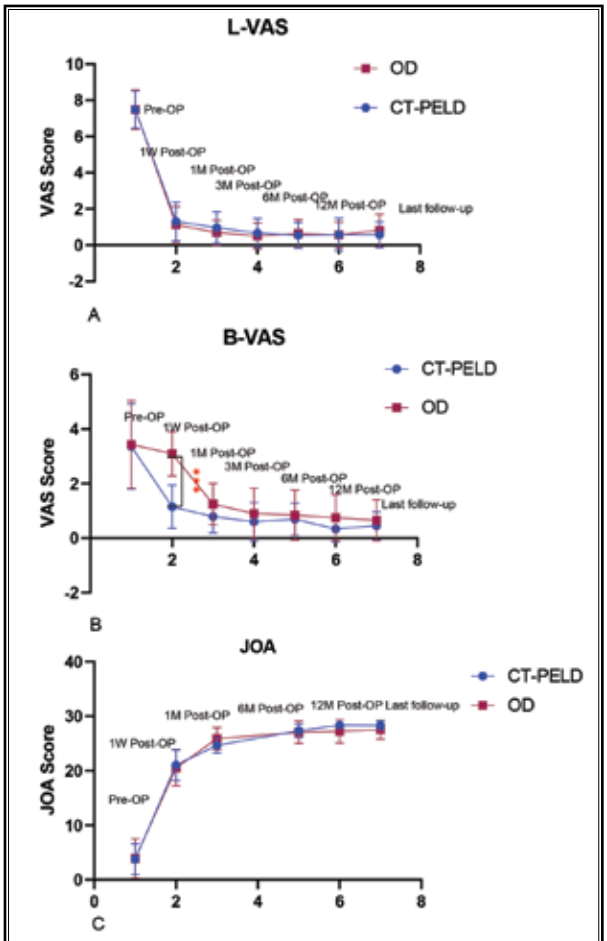

Fig. 1. *Clinical results of the CT-PELD and OD groups.* A: *The L-VAS score of the 2 groups postoperatively is significantly lower than that preoperatively (P < 0.01), and no significant difference was found between the groups.* B: *The B-VAS score post-operation in both groups was significantly lower than that pre-operation (P < 0.01), while the B-VAS score at one week post-operation in the OD group was higher than that in the CT-PELD group (P < 0.01).* C: *The JOA score of the 2 groups was significantly higher post-operation than pre-operation (P < 0.01), while no obvious difference was found between the groups.*

in the serum concentration of CRP pre- and post- surgery in the CT-PELD group. However, in the OD group, the concentration of CRP was elevated at 48 hours and one week after surgery, and the peak value was observed at 48 hours after surgery (Fig. 5).

Discussion

The incidence of nucleus pulposus migration, including low migration and high migration, is 35% – 72% according to the literature (12,13). For highly migrated herniations, PELD guided by 2-D fluoroscopy remains questionable because of anatomical barriers; conventional open surgery is recommended for this situation. Advanced operative imaging using CT navigation has been developed more recently and shows promise for replacing fluoroscopy as the preferred intraoperative imaging technique because it presents the dynamic anatomy of the operative target region and positional relationship between the instrument and lesion. However, to our knowledge, no study has quantitatively compared the clinical outcomes and traumatic and inflammatory effects between CT-PELD and traditional OD. We performed a prospective randomized study to compare the traumatic and inflammatory effects and clinical outcomes between CT-PELD and OD for HLDH patients.

In the current study, we compared the clinical outcomes between CT-PELD and OD for treating HLDH. These 2 approaches were both effective according to the operative results measured by the pre- and post-

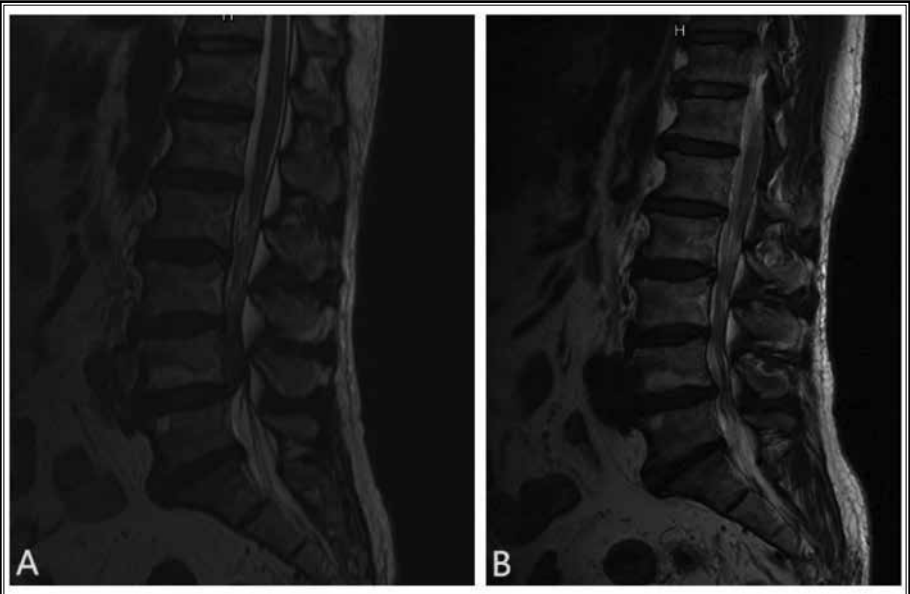

Fig. 2. A: *Sagittal preoperative MRI shows highly upward migrated lumbar disc herniation at the L4/5 level.* B: *Six-month postoperative MRI shows that the migrated protrusion of L4/5 level was removed.*

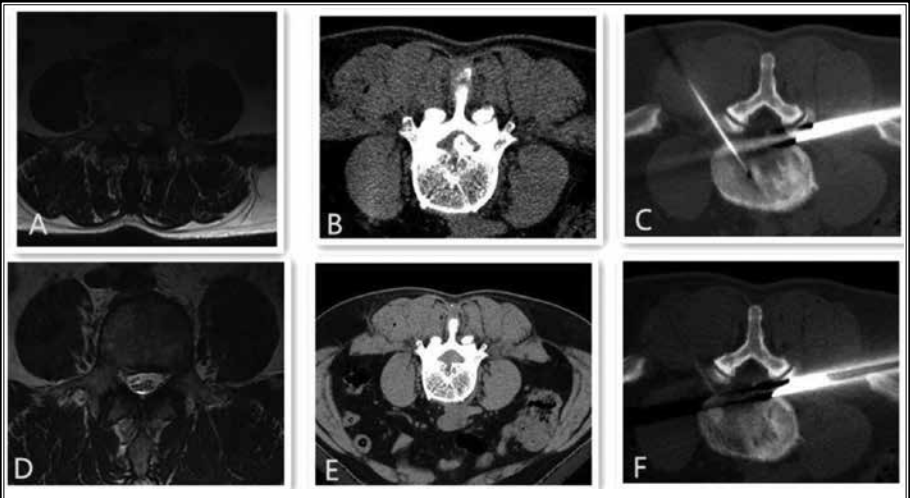

Fig. 3. *Intraoperative CT guidance and postoperative CT scan diagrams.* A: *Transverse preoperative MRI shows that the protrusion migrated to spinal canals, and the spine and nerve root has been compressed.* D: *Six-month postoperative transverse MRI shows that the protrusion was removed.* B: *Intraoperative CT shows the enhancement protrusion after contrast medium injection.* E: *CT immediately after operation shows that the position disappeared.* C, F: *Intraoperative CT shows the location of the work channel during operation.*

operative VAS and JOA scores, as well as the modified MacNab criteria. However, the VAS score at one week after surgery in the CT-PELD group was superior to that in the OD group, demonstrating that CT-PELD has better back pain relief than OD at the acute phase post-operation. In the OD group, one patient developed surgical incision infection 4 days postoperatively, and one patient had cauda equina injury before surgery and persistent numbness in the saddle area 13 months after surgery. In the CT-PELD group, one patient developed recurrence at 2 years post-operation and received secondary surgery.

Choi et al (14) and Kim et al (15) used the PELD technique for HLDH, and these 2 studies presented remnant disc material rates of 5.08 (3/59) and 13% (7/53), respectively. Nucleus pulposus residue is associated with the characteristics of a highly migrated nucleus pulposus. Specifically, these highly migrated nucleus pulposi are usually multi-fragmented and difficult to detect by preoperative radiology examination. With CT navigation, the presence of remnant disc material can be found promptly and addressed directly during the operation; therefore, in the present study, no patient had nucleus pulposus residue after surgery, making the rate presented here lower than that previously reported. Wu et al (16) performed 2-level PELD for single-level HLDH and reported outcomes that were comparable to those in the present study.

We quantitatively compared the levels of TNF-α and IL-6 (inflammatory cytokines) in the sera of HLDH patients pre-operation, immediately post-operation, and 48 hours and one week post-operation between the 2 groups. No significant differences were found in inflammatory cytokines or

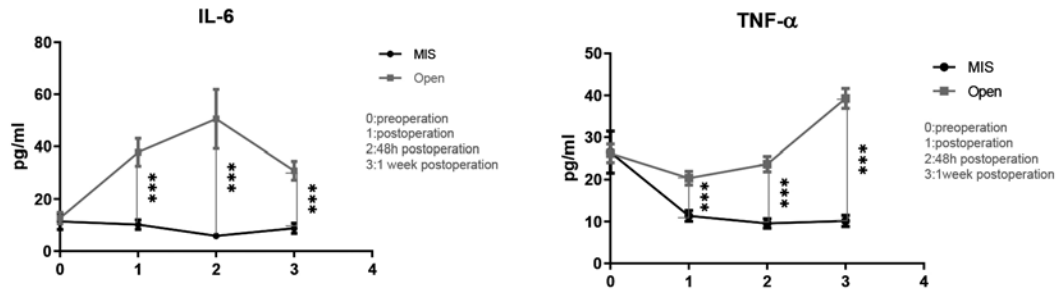

Fig. 4. *Serum concentrations of IL-6 (pg/ml) and TNF-α (pg/ml) pre- and post-operation in the CT-PELD and OD groups.* A: *The serum concentration of IL-6 in the CT-PELD group post-operation was not significantly different from that in the CT-PELD group pre-operation. However, in the OD group, the serum concentration of IL-6 post-operation was significantly higher than that pre-operation ($P < 0.01$) and peaked 48 hours post-operation. The serum concentration of IL-6 in the OD group post-operation was higher than that in the CT-PELD group ($P < 0.01$).* B: *The serum concentration of TNF-α in the CT-PELD group was lower than that pre-operation, while the TNF-α concentration in the OD group was significantly higher than that pre-operation and one week post-operation. The serum TNF-α concentration was significantly higher in the OD group than in the CT-PELD group ($P < 0.01$).*

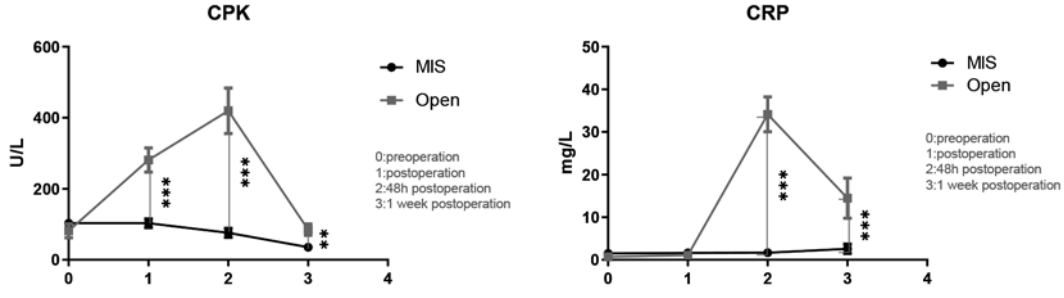

Fig. 5. *Serum concentrations of CPK (U/L) and TNF-α (mg/L) pre- and post-operation in the CT-PELD and OD groups.* A: *The serum concentration of CPK (U/L) in the CT-PELD group was significantly lower post-operation than pre-operation ($P < 0.01$), while the serum concentration of CPK in the OD group was significantly higher post-operation than pre-operation ($P < 0.01$), with a peak appearing 48 hours post-operation that gradually decreased. The serum concentration of CPK in the CT-PELD group was lower than that in the OD group.* B: *In the CT-PELD group, no significant difference was found in the serum concentration of CRP pre- and post-operation. However, in the OD group, the serum concentration of CRP was higher 48 hours post-operation than pre-operation ($P < 0.01$), peaked and then gradually decreased thereafter. The CRP concentration was higher in the OD group 48 hours and one week post-operation than in the CT-PELD group ($P < 0.01$).*

trauma indicators before surgery between the 2 groups. In the CT-PELD group, the serum levels of TNF-α and IL-6 postoperatively were significantly lower than those preoperatively; however, in the OD group, the serum level of IL-6 increased within 48 hours after surgery and then decreased one week after surgery. In addition, the serum level of TNF-α in the OD group increased both at 48 hours and one week postoperatively. The serum value of TNF-α and IL-6 was significantly lower in CT-PELD group than in the OD group immediately postoperatively and 48 hours and one week postoperatively.

Previous studies have revealed that proinflammatory cytokines may be associated with the mechanisms underlying the development of chronic pain after disc herniation, and cytokine reduction during the early phase may also reflect treatment (17). Moreover, the blood protein levels of the proinflammatory cytokine TNF-α shows a positive correlation with pain intensity according to a recent study. The current study showed that the serum levels of proinflammatory cytokines TNF-α and IL-6 were significantly lower in the CT-PELD group than in the OD group in the early post-operative phase, quantitatively demonstrating that CT-PELD has a minor influence on the inflammatory reaction and better pain relief in patients with HLDH. CT-PELD is a minimally invasive technique with a smaller surgi-

cal incision, less tissue damage, faster pain relief, and faster recovery than OD; therefore, proinflammatory cytokines are produced at lower levels. Pain intensity was higher in the OD group at the early phase after surgery, likely attributed to the higher level of proinflammatory factors (18). These results are consistent with those from previous reports (19,20) and may provide new quantitative evidence regarding the lower levels of proinflammatory cytokines associated with CT-PELD to indicate its minimally invasive nature.

The serum levels of CPK and CRP increased 48 hours after surgery and then decreased one week post-operation in the OD group. However, no difference was found in the CPK and CRP levels in the CT-PELD group pre- or post-operatively. Muscle injury during spine surgery is directly related to the retraction time and external compression force applied by the retractor. The serum activity of CPK has been extensively studied and is considered a qualitative marker for skeletal muscle trauma (18). The serum CPK concentration in the CT-PELD group was significantly lower than that in the OD group, indicating that CT-PELD with minor muscle extrusion and damage results in less trauma during surgery. OD is thought to affect the musculature (mainly the paravertebral muscles) more deeply, often causing high levels of CK at the early post-operative phase. These results agree with those from previous studies. Zhang and coworkers found a reduced increase in total CPK after microdiscectomy compared with the open approach, with a peak in enzyme activity 24 hours after surgery (19). Kim et al (20) showed that, after L4-L5 single-level decompression and arthrodesis for lumbar spinal stenosis (PUF), the total CK concentrations were higher in the open-operated group than those in the mini-operated group. In both cases, however, the increase in CK activity returned to the basal level 7 days after surgery. The current study quantitatively evaluated the serum level of CK in CT-PELD and compared it to that in OD, revealing that CT-PELD does not affect CK activity; however, OD could increase CK activity.

Limitation

Because of the strict criteria for patient selection, the study sample size was relatively small. Thus, the identified differences and statistical power should be confirmed in a larger cohort that considers different lesion levels.

Conclusion

Current evidence indicates that the clinical outcomes of CT-PELD are equivalent to those of OD and that these 2 techniques are safe and effective procedures for HLDHs. However, CT-PELD is associated with minor trauma and has a minor impact on the inflammatory reaction for HLDH treatment.

Authors' Contributions

Bing R wrote the draft of the manuscript and participated in the surgical and medical treatment. Jun W performed the surgery, coordinated and helped to draft and finalize the manuscript. Qiong Z, Jun Y, Xin-Rong C, and XinYuan W participated in the surgical and medical treatment and followed up the patient. Jian W and Yong L collected the serum sample and performed the ELISA experiment. All authors read and approved the final manuscript.

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