Endoscopic removal of nucleus pulposus of intervertebral disc on lumbar intervertebral disc protrusion and the influence on inflammatory factors and immune function

GANG XU[1], CHANGCHUN ZHANG[1], KUN ZHU[1], ZHENGQI BAO[1], PINGHUI ZHOU[1] and XIAOJUN LI[2]

[1]Department of Orthopedics, The First Affiliated Hospital of Bengbu Medical College, Bengbu, Anhui 233004;
[2]Department of Spine, Wuxi Traditional Chinese Medicine Hospital, Wuxi, Jiangsu 214071, P.R. China

Abstract. Endoscopic removal of nucleus pulposus (NP) of intervertebral disc (IVD) on lumbar intervertebral disc protrusion (LIDP) and its influence on inflammatory factors and immune function were explored. A total of 145 patients with LIDP admitted to The First Affiliated Hospital of Bengbu Medical College from June 2017 to December 2018 were selected and electively treated, in which 87 patients were treated with fenestration discectomy (fenestration group) and 58 patients were treated with endoscopic removal of NP of IVD (minimally invasive group). Effects on patients in the two groups within 6 months after surgery were evaluated by modified MacNab score; differences in surgical related indexes and incidence rates of complications between the two groups were compared; the Oswestry dysfunction score and VAS pain score before treatment, and 1, 3 and 6 months after treatment, and changes of cellular levels of TNF-α, IL-4, IL-6, CD3$^+$, CD4$^+$, and CD8$^+$ before treatment, and 24 and 48 h after surgery were evaluated. Length of surgical incision, intraoperative blood loss, time of operation, time in bed, and hospital stays of patients in minimally invasive group were lower than those in the fenestration group (P<0.05). The Oswestry score and VAS score of patients in minimally invasive group 1, 3 and 6 months after surgery were lower than those in fenestration group (P<0.05). The incidence rate of spinal instability and overall incidence of complications of patients in minimally invasive group were significantly lower than those in fenestration group (P<0.05). Levels of TNF-α and IL-6 of patients in the minimally invasive group 24 and 48 h after surgery were lower than those in the fenestration group (P<0.05) and cellular levels of IL-4, CD3$^+$, CD4$^+$, and CD8$^+$ were higher (P<0.05). In conclusion, endoscopic removal of NP of IVD has good therapeutic effects in patients with LIDP. It reduces inflammation and suppresses immune function with higher safety, worthwhile for clinical use.

Introduction

Lumbar intervertebral disc protrusion (LIDP) is usually caused by degenerative changes of contents of intervertebral disc (IVD), such as nucleus pulposus (NP) and annulus fibrosus, it often occurs in the posterolateral region and is the main cause of low back pain. It shows high incidence rate and causes high medical expenses, thus increasing social and family burdens (1,2). Lumbar discectomy is still one of the best choices for patients who failed in conservative treatment, and advantages of surgical treatment include its quick effects on the improvement of symptoms and its good long-term efficacy (3,4). However, the incidence rate of reherniation of IVD in patients undergoing surgery is still 3-18%, which is the most important reason for most patients to receive lumbar discectomy again, and patients are 10 times more likely to have future spinal surgery than standard care patients (5,6). Therefore, choices of surgical methods are of great significance in clinical practice.

Traditional fenestration discectomy involves a large number of normal bones, muscle tissues, and small joints, which causes great damage to the stability of spinal structure of patients. Lumbar segmental instability is one of the causes of failure of lumbar surgery (7,8). With the continuous development of minimally invasive amplification technology and the renewal of minimally invasive concepts, minimally invasive surgery has been applied to various surgical treatments and has achieved good effects (9). The application of endoscopic discectomy in the clinical treatment of lumbar intervertebral disc protrusion (LIDP) is increasing, which significantly reduces the damage to patients and maximizes the stability of

Correspondence to: Dr Xiaojun Li, Department of Spine, Wuxi Traditional Chinese Medicine Hospital, 8 Zhongnan West Road, Wuxi, Jiangsu 214071, P.R. China
E-mail: xbhp15@163.com

the spinal structure (10,11). However, its efficacy has not been widely recognized clinically.

Therefore, this study analyzed effects of endoscopic removal of NP of IVD on LIDP again, as well as its influences on inflammatory factors and immune function, so as to provide references for clinical treatment of LIDP.

Patients and methods

Objects of study. A total of 145 patients with LIDP aged between 30 and 60 years were admitted to The First Affiliated Hospital of Bengbu Medical College (Bengbu, China) from June 2017 to December 2018 were selected and were electively treated. Patients were divided into two groups according to different treatment methods. There were 87 patients treated with fenestration discectomy (fenestration group) and 58 patients treated with endoscopic removal of NP of IVD (minimally invasive group). The inclusion criteria were as follows: Patients diagnosed as LIDP by X-ray imaging and met the diagnostic criteria of LIDP (12); patients failed in conservative treatment, with no spondylolisthesis and spinal stenosis. The exclusion criteria were as follows: Patients experienced recurrence of LIDP, or with previous history of surgery and multi-segmental protrusion of IVD; patients with LIDP combined with diabetes, hypertension, congenital spinal deformity, greater bone compression, bone metabolic disease, tumor, severe infection, hemophilia or other coagulation diseases.

This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Bengbu Medical College. Signed informed consents were obtained from the patients or the guardians.

Surgical methods. Patients in the fenestration group underwent general anesthesia in lateral posture. The location of lesion was localized by X-ray after successful anesthesia. The skin was incised on the fourth to the first spinous process. Surrounding tissues were bluntly separated to show ligamentum flavum, and en bloc excision of ligamentum flavum was performed. Nerve roots and dura mater were separated by epidural detacher; longitudinal ligament and annulus fibrosus were cut after exposing IVD; herniated NP was pulled out by nerve root retractor; diseased tissues were removed and the blood was stopped from flowing. Local anesthesia was adopted in the minimally invasive group. The needle was inserted into vertebral posterior or the center of the pedicle of vertebral arch under the guidance of X-ray, and the needle was inserted through the intervertebral foramen to the intervertebral space [2 ml suspension of omnipaque and methylthioniniumchloride (6:1)]; and then radiography was performed, guidewire was inserted, puncture needles were out and catheter was put in; devices such as intervertebral foramen were connected, the working channel of intervertebral foramen was 8 mm; flocculent substances and fat were cleaned; loose NP was removed and the blood was stopped from flowing after no leakage.

Observation indicators. The efficacy of patients in the two groups within 6 months after surgery was evaluated by the modified MacNab score. Differences in surgical related indexes (length of incision, intraoperative blood loss, time of operation, time in bed, hospital stays) of patients were compared between the two groups. The Oswestry dysfunction score (pain in back and loin, leg pain, ability of daily life, lifting, walking, sitting, standing) and VAS pain score of patients were evaluated before surgery and 1, 3 and 6 months after surgery. The incidence rate of complications of patients was counted in the two groups. Changes of inflammatory factors (TNF-α, IL-4, IL-6) and immune function (CD3$^+$, CD4$^+$ and CD8$^+$ cells) of patients between the two groups were compared before surgery, 24 and 48 h after surgery.

Detection methods. The fasting peripheral blood of patients was collected in the early morning. After heparin anticoagulation, serum was centrifuged at 100 x g at 4°C for 10 min to detect inflammatory factors of patients. Levels of TNF-α, IL-4 and IL-6 were all detected by ELISA. The detection kits were purchased from Abcam, with cat. nos. ab181421, ab46022 and ab46027, respectively. Altogether 20 μl samples or standard products were added into 96-well plates and negative controls were set. Each sample was provided with three parallel wells, water bath was carried out at 37°C for 30 min after sealing the membrane, excess liquid was poured out, washing buffer was used 3 times, each time for 30 sec, and enzyme-labeled antibody was added. Then, the above steps were repeated for incubation and washing, 50 μl of developer A and B were successively added, they were developed at 37°C in the dark for 15 min, 50 μl of stopping solution was added to terminate the reaction, absorbance of the samples was measured within 15 min with 450 nm measuring wavelength. The microplate reader was purchased from Beijing Putian Xinqiao Technology Co., Ltd. CD3$^+$, CD4$^+$ and CD8$^+$ cells were detected by Attune NxT flow cytometer and purchased from Thermo Fisher Scientific, Inc., and relevant reagents and instruments were supplied by Thermo Fisher Scientific, Inc.

Statistical analysis. SPSS 19.0 (SPSS, Inc., Chicago, IL, USA) was adopted. The measurement data were expressed as [n (%)], and comparison of ratios between the two groups was tested by χ^2 test. The enumeration data were expressed as mean ± standard deviation (mean ± SD), and the comparison between the two groups was performed by independent-samples t-test. The comparison of different time points in the group was performed by repeated measures analysis of variance, and the post hoc test was performed by LSD test. P<0.05 was considered to indicate a statistically significant difference.

Results

General data. There were 87 patients in the fenestration group, including 48 males (55.17%) and 39 females (44.83%), aged 36.75±5.48 years. There were 58 patients in the minimally invasive group, including 34 males (58.62%) and 24 females (41.38%), aged 38.16±5.93 years. There were no statistical differences in ratios of sex and age between the two groups (P>0.05), neither any significant difference in other data such as body mass index (BMI), course of disease, and pathological segments between them (P>0.05) (Table I).

Clinical efficacy. There were no significant differences in rates of excellent, good, acceptable, and poor efficacy of patients between the two groups (P>0.05) (Table II).

Table I. General data.

Variables	Fenestration group (n=87)	Minimally invasive group (n=58)	χ^2/t	P-value
Sex [n (%)]			0.168	0.682
Male	48 (55.17)	34 (58.62)		
Female	39 (44.83)	24 (41.38)		
Age (years)	36.75±5.48	38.16±5.93	1.469	0.144
BMI (kg/m^2)	23.75±3.14	23.48±3.86	0.462	0.645
Course of disease (years)	1.04±0.12	1.06±0.14	0.919	0.360
Pathologic segments [n (%)]			1.394	0.498
L3-L4	10 (11.49)	6 (10.34)		
L4-L5	45 (51.72)	25 (43.10)		
L5-S1	32 (36.78)	27 (46.55)		
Prominent types [n (%)]			0.065	0.799
Central type	18 (20.69)	11 (18.97)		
Peripheral type	69 (79.31)	47 (81.03)		
Straight leg raising test [n (%)]			0.115	0.734
Positive	44 (50.57)	31 (53.45)		
Negative	43 (49.43)	27 (46.55)		
Combined with paresthesia [n (%)]			0.105	0.746
Yes	19 (21.84)	14 (24.14)		
No	68 (78.16)	44 (75.86)		
Combined with abnormal movements [n (%)]			0.070	0.791
Yes	15 (17.24)	11 (18.97)		
No	72 (82.76)	47 (81.03)		

BMI, body mass index.

Table II. Analysis of clinical efficacy of patients in the two groups [n (%)].

Variables	Fenestration group (n=87)	Minimally invasive group (n=58)	χ^2	P-value
Excellent	46 (52.87)	36 (62.07)	1.198	0.274
Good	28 (32.18)	17 (29.31)	0.134	0.714
Acceptable	9 (10.34)	4 (6.90)	0.507	0.476
Poor	4 (4.60)	1 (1.72)	0.863	0.353

Analysis of surgical related indicators. Length of surgical incision, intraoperative blood loss, time of operation, time in bed, and hospital stays of patients in minimally invasive group were lower than those in fenestration group (P<0.05) (Fig. 1).

Analysis of Oswestry dysfunction. There were no statistical differences in the Oswestry score of patients between the two groups before surgery (P>0.05). The Oswestry score of patients in the two groups continuously decreased 1, 3 and 6 months after surgery (P<0.05), and the Oswestry score of patients in minimally invasive group was lower than those in fenestration group 1, 3 and 6 months after surgery (P<0.05) (Fig. 2).

Results of VAS score. There were no significant differences in the VAS score of patients between the two groups before surgery (P>0.05). The VAS score of patients in the two groups continuously decreased 1, 3 and 6 months after surgery (P<0.05), and the VAS score of patients in the minimally invasive group was lower than those in the fenestration group 1, 3 and 6 months after surgery (P<0.05) (Fig. 3).

Analysis of the incidence rate of complications in the two groups. The incidence rate of spinal instability of patients in minimally invasive group was significantly lower than that in fenestration group (P<0.05). There were no statistical differences in the incidence rate of incision infection and transient nerve paralysis (P>0.05). The incidence rate of complications of patients was also higher than that in minimally invasive group (P<0.05) (Table III).

Analysis of levels of inflammatory factors after surgery of patients in the two groups. Levels of TNF-α, IL-4 and IL-6 of

Table III. Analysis of incidence rate of complications of patients in the two groups [n (%)].

Variables	Fenestration group (n=87)	Minimally invasive group (n=58)	χ^2	P-value
Incision infection	7 (8.05)	3 (5.17)	0.448	0.504
Transient nerve paralysis	10 (11.49)	2 (3.45)	2.003	0.157
Spinal instability	7 (8.05)	0 (0.00)	Fisher	0.042
Total complications	24 (27.59)	5 (8.62)	7.823	0.005
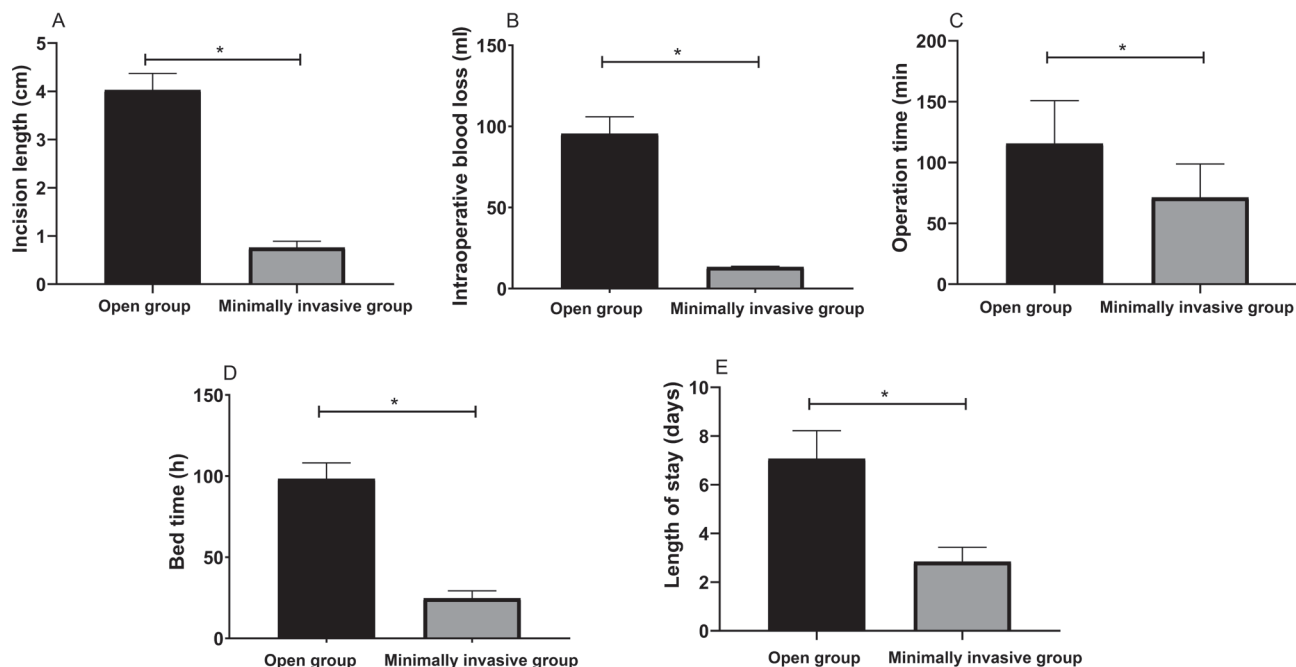
Figure 1. Analysis of surgical related indicators. (A) Length of surgical incision. (B) The amount of intraoperative blood loss (C) Time of operation. (D) Time in bed. (E) Hospital stays. *P<0.05.
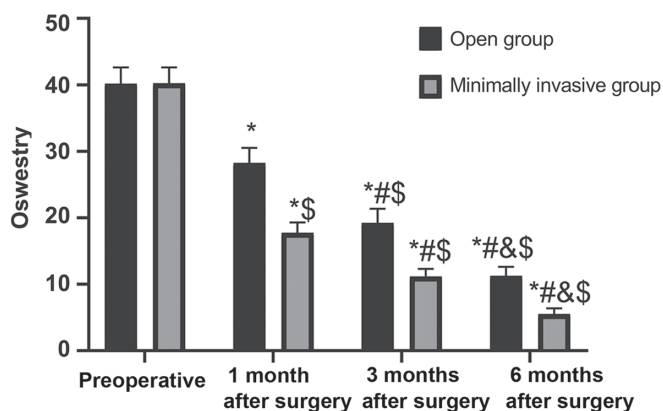

Figure 2. Analysis of Oswestry dysfunction. *P<0.05 compared with that of before surgery; #P<0.05 compared with that of 1 month after surgery; &P<0.05 compared with that of 3 months after surgery; $P<0.05 in the fenestration group at same time.
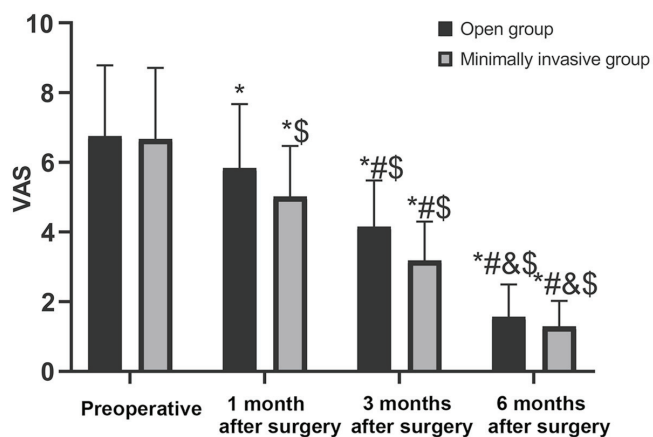

Figure 3. VAS scores. *P<0.05 compared with that of before surgery; #P<0.05 compared with that of 1 month after surgery; &P<0.05 compared with that of 3 months after surgery; $P<0.05 in the fenestration group at the same time.

patients in the two groups were not significantly different before surgery (P>0.05). Levels of TNF-α and IL-6 of patients in the two groups continuously decreased 24 and 48 h after surgery (P<0.05). Levels of IL-4 continued to rise (P<0.05); however, levels of TNF-α and IL-6 of patients in minimally invasive

group after surgery were lower than those in fenestration group (P<0.05) and levels of IL-4 were higher (P<0.05) (Table IV).

Changes in postoperative immune function of patients in the two groups. There were no statistical differences in cellular

Table IV. Analysis of levels of inflammatory factors after surgery of patients in the two groups (pg/ml).

Variables	Fenestration group (n=87)	Minimally invasive group (n=58)	t	P-value
TNF-α				
Before surgery	90.24±9.64	91.19±9.14	0.593	0.554
24 h after surgery	68.42±5.25[a]	50.13±4.86[a]	21.164	<0.001
48 h after surgery	51.24±3.43[a,b]	20.02±2.73[a,b]	58.106	<0.001
IL-4				
Before surgery	24.28±3.12	23.83±2.87	0.878	0.381
24 h after surgery	35.22±3.02[a]	46.48±1.85[a]	25.381	<0.001
48 h after surgery	40.24±1.88[a,b]	49.22±1.83[a,b]	28.477	<0.001
IL-6				
Before surgery	234.58±28.64	233.76±27.15	0.172	0.863
24 h after surgery	164.73±20.42[a]	131.68±17.15[a]	10.163	<0.001
48 h after surgery	92.19±14.32[a,b]	60.47±12.36[a,b]	13.787	<0.001

[a]P<0.05 compared with that of before surgery; [b]P<0.05 compared with that of 24 h after surgery.

Table V. Changes in postoperative immune function of patients in the two groups (%).

Variables	Fenestration group (n=87)	Minimally invasive group (n=58)	t	P-value
CD3				
Before surgery	58.67±14.75	59.43±13.43	0.315	0.753
24 h after surgery	51.36±10.57[a]	55.83±11.39[a]	2.398	0.018
48 h after surgery	55.85±10.42[b]	59.86±10.27[b]	2.283	0.024
CD4				
Before surgery	31.47±7.66	30.75±8.15	0.540	0.590
24 h after surgery	24.13±9.07[a]	28.48±8.39[a]	2.914	0.004
48 h after surgery	29.17±9.83[b]	32.82±11.28[b]	2.064	0.041
CD8				
Before surgery	25.12±9.17	25.85±9.22	0.524	0.601
24 h after surgery	16.04±7.25[a]	20.79±8.64[a]	3.928	<0.001
48 h after surgery	12.87±5.69[a,b]	17.13±6.11[a,b]	4.759	<0.001

[a]P<0.05 compared with that of before surgery; [b]P<0.05 compared with that of 24 h after surgery.

levels of CD3+, CD4+, and CD8+ of patients between the two groups before surgery (P>0.05). Cellular levels of CD3+, CD4+, and CD8+ in the two groups 24 h after surgery were lower than those before surgery (P<0.05). CD3+ and CD4+ cells in the two groups 48 h after surgery recovered to preoperative similar level (P>0.05), which were higher than those at 24 h after surgery (P<0.05). But cellular levels of CD8+ continued to decrease (P<0.05). Cellular levels of CD3+, CD4+, and CD8+ of patients in minimally invasive group were higher than those in fenestration group 24 and 48 h after surgery (P<0.05) (Table V).

Discussion

LIDP is an increasingly serious public health problem characterized by increased fibrosis, decreased content of proteins and

polysaccharides, reduced ability of tissue binding and water retention, and impaired mechanical properties of the motor segment. Its recurrence rate ranges from 5 to 25% (13,14). Safe and effective surgical treatment of LIDP is of great importance to surgeons. Minimally invasive surgery has always been an important research direction for surgical treatment. This study analyzed the therapeutic value of endoscopic discectomy in patients with LIDP.

The results of this study showed that there were no differences in clinical effects of the two surgical methods, but the incidence rate of postoperative complications after minimally invasive surgery was significantly lower than that after fenestration surgery, especially the incidence rate of spinal instability. Spinal instability is the main complication after surgery of fenestration discectomy. Fenestration discectomy requires extensive resection of bone tissues and ligaments, so

patients after it often require fixation of additional surgical instruments to reduce postoperative spinal instability (15), which can be avoided with endoscopic discectomy. The spinal canal can fully enter the midline of the spinal canal without extensive resection of the small joint or adjacent pedicle. In the present study of Li *et al* (16), IVD total endoscopic surgery of L5/S1 through lamina was a safe, reasonable and effective minimally invasive spinal surgery technique with good short-term clinical efficacy. Similar results were reported in another study (17). There were no significant changes in the height of IVD of patients under percutaneous endoscopic lumbar discectomy, and the height of IVD was significantly reduced from 23.7±3.3 to 19.1±3.7 in patients with fenestration discectomy. The study also showed that the minimally invasive group experienced significantly shorter time of surgery, hospitalization and returning to work, which was similar to our results. Our results also showed that the length of incision, amount of intraoperative blood loss, time of operation, time in bed, and hospital stays in minimally invasive group were lower than those in fenestration group. Similar conclusions were found in the study of Garg *et al* (18): The amount of bleeding and hospital stays were significantly shorter in patients undergoing microendoscopic discectomy. These indicators are related to surgical safety. Chen *et al* (19) indicated that percutaneous endoscopic discectomy had better safety and was associated with less blood loss, shorter hospital stays, and short incision, and was the best choice for patients with LIDP. Pan *et al* (20) also compared endoscopic lumbar discectomy with traditional lumbar discectomy in patients with LIDP. In their results, patients in the endoscope group were significantly more satisfied with the treatment than those in the traditional treatment group, and the bleeding volume, hospital stays, and wound size in the endoscope group were also smaller than those in the traditional treatment group. In addition, they also found that the improvement of inflammatory cytokines IL-6 and CPR in the endoscope group at 24 and 48 h after surgery was significantly better than that in the traditional treatment group, which was similar to our results. However, they did not find any difference in the incidence rate of complications between the two groups. Only one case of numb nerve occurred in the endoscope group and recovered after 2 weeks, while no complications occurred in the traditional treatment group. The incidence rate of complications after discectomy reportedly ranges from 13.2 to 19.3% (21), which requires further analysis of more factors, such as the proficiency of surgical operators, surgical approach, postoperative nursing and so on.

Another interesting finding of this study was that patients in minimally invasive group had lower levels of postoperative inflammatory response and faster immune function recovery. Chang *et al* (22) drew similar conclusions in their study. The levels of inflammatory factors TNF-α and CRP in patients undergoing percutaneous endoscopic lumbar discectomy were also significantly lower than those in patients undergoing open discectomy. We speculated that this was related to postoperative pain in patients. Pain of the patients with IVD protrusion after the NP removal was reduced, the compression nerve and the local inflammation caused by it were also reduced. Therefore, the degree of inflammation is an indirect indicator for judging effects of surgery (23). In some studies, it has been reported that increased inflammatory response caused

by surgical stress is an important cause of postoperative pain in patients because inflammatory factors are also important mediators of pain (24). In a basic study, pain behavior was increased after injection of TNF-α in IVD puncture model of mice (25). The Oswestry score can assess functions of pain in back and loin, leg pain, ability of daily life, lifting, walking, sitting, and standing (26). In our results, the Oswestry score in the minimally invasive group was significantly better than those in fenestration group at 1, 3 and 6 months after surgery. Results of further analysis of pain also showed that the degree of postoperative pain of patients in minimally invasive group was significantly lower than that in fenestration group. In the study of Liu and Wang (27), it was also found that percutaneous endoscopic discectomy could effectively treat LIDP, which was beneficial to reduce pain and inflammation. However, there are few reports on effects of these two surgical methods on postoperative immune function. Postoperative pain could cause immunosuppression and lead to decreased immune function in patients (28). The minimally invasive group experienced lower postoperative pain, so the degree of inhibition of immune function was lower. This result was also confirmed by our studies. Although cellular levels of CD3+, CD4+, and CD8+ in the two groups were decreased 24 h after surgery, the minimally invasive group had significantly higher levels than the fenestration group.

The deficiency of this study was that a prospective analysis was adopted. Although we set strict inclusion criteria, there still may be some bias in the inclusion process of patients. This study only analyzed the short-term efficacy of patients in the two groups, and the long-term efficacy results still need further tracking.

In conclusion, endoscopic removal of NP of IVD has good therapeutic effects in patients with LIDP, and can reduce inflammation and suppression of immune function with higher safety, which is worthy of clinical use.

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

GX observed the indicators and wrote the manuscript. XL interpreted and analyzed the patient data. CZ and KZ designed the study and performed the experiments. ZB and PZ were responsible for the analysis and discussion of the data. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of The First Affiliated Hospital of Bengbu Medical College (Bengbu, China). Signed informed consents were obtained from the patients or the guardians.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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