

Original Article

Collagenase chemonucleolysis versus percutaneous endoscopic discectomy for extraforaminal lumbar disc herniations

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Abstract: Objective: To compare the advantages and disadvantages of collagenase chemonucleolysis and percutaneous endoscopic discectomy (PED) in the management of extraforaminal lumbar disc herniation. Methods: In this non-randomized controlled clinical trial, a total of 49 patients who were diagnosed with extraforaminal lumbar disc herniation were assigned to undergo either PED (n=22) or collagenase chemonucleolysis (n=27). The primary outcomes were pain improvements (VAS scores), therapeutic efficacy (improved MacNab criteria) and the incidence of complications within 6 months after operation; and the secondary outcomes included intraoperative pain symptoms, operation duration, the time for postoperative bed rest and the costs for hospitalization. Results: The preoperative basic information was similar among the patients in both groups ($P>0.05$). Besides, no significant differences in postoperative Visual Analogue Scale (VAS) score at two weeks, three months, and six months, as well as in the postoperative therapeutic efficacy at six months respectively were found between both groups ($P>0.05$). Neither groups had severe complications ($P>0.05$). The patients with collagenase chemonucleolysis had longer bed rest duration, but fewer costs for hospitalization, shorter operation time, less intraoperative pain compared with the PED patients ($P<0.001$). Conclusion: Collagenase chemonucleolysis is safe and effective for extraforaminal lumbar disc herniations, and has the advantages of immediate relief of intraoperative pain, reduced costs for hospitalization, and simpler operation.

Keywords: Collagenase chemonucleolysis, percutaneous endoscopic discectomy (PED), extraforaminal lumbar disc herniation, VAS score, improved MacNab criteria

Introduction

Extraforaminal lumbar disc herniation accounts for 2.6-11.7% of all lumbar disc herniations (LDH) [1]. The herniation causes a small range of movability and tends to be compressed by the herniated nucleus pulposus due to its closeness to dorsal root ganglions and the constraint of extraforaminal nerve root from pedicle and intervertebral foramen ligaments, mostly leading to severe radicular pains and nerve damages in varied degrees [2, 3]. Only 10% of the patients with extraforaminal lumbar disc herniation feel satisfied with conservative treatment, and most of the patients require surgery [4]. Traditional open surgery may cause damages to the articular process and lumbosacral muscles, or lead to secondary lumbar

instability or lumbosacral pains [5]. Percutaneous endoscopic discectomy (PED) is effective for the treatment of extraforaminal lumbar disc herniations [6-11]. Compared with open surgeries, it is characteristic of less damage to the muscles and the articular processes in the lumbar-sacral region under local anesthesia [6].

Minimally invasive treatments, including chemonucleolysis, are effective in the treatment of lumbar disc herniations and characteristic of less damage to the muscles and the articular processes in the lumbar-sacral region under local anesthesia [12].

In China, collagenase has been the major agents in lumbar disc chemonucleolysis [13]. Recently, only a few studies on collagenase

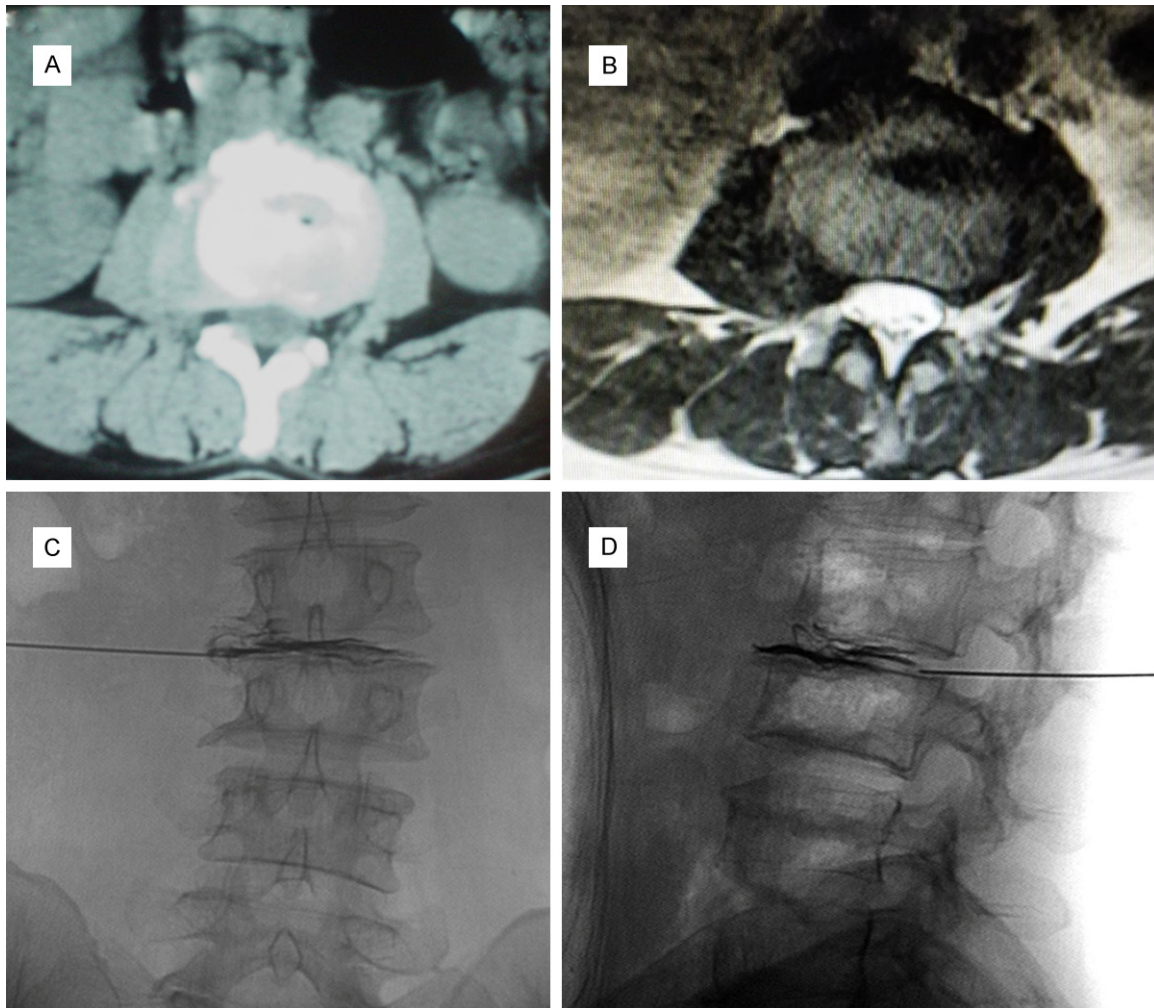


Figure 1. Images of the collagenase chemonucleolysis and radiographs of the lateral lumbar spine with position of needle tip and dispersion of contrast agents shot before the puncture and drug injection. A, B: Lumbar disc CT and lumbar cross-sectional MRI suggested L2/3 extraforaminal lumbar disc herniation; C, D: Opacification revealed in the position punctured by the needle and in herniation after angiography.

chemonucleolysis in treatment of extraforaminal lumbar disc herniation have been involved in its mid and long term therapeutic efficacy and complications. However, few studies are specifically focused on its comparison with other protocols [14]. In the present study trial, the advantages and disadvantages of collagenase chemonucleolysis and PED were compared in the treatment of extraforaminal lumbar disc herniations.

Methods

General information of the patients

This non-randomized controlled clinical trial was approved by the Ethics Committee of the

First Affiliated Hospital of Nanchang University. Subjects were selected from the patients with extraforaminal lumbar disc herniation treated in the Pain Department of the mentioned hospital from August 2012 to February 2016. Inclusion criteria for this trial: the patients with such symptoms as nerve root pain or numbness, more severe pain in lower limbs than in low back, positive in straight leg raising test and femoral nerve stretching test, or pains induced by unilateral clearance for extraforaminal lumbar disc herniation as documented on imaging or clinical practices. Exclusion criteria: the patients with such puncture contra indications as surgical history at the same lumbar segments, herniation calcification, spondylolisthesis, intervertebral foramen stenosis, associ-

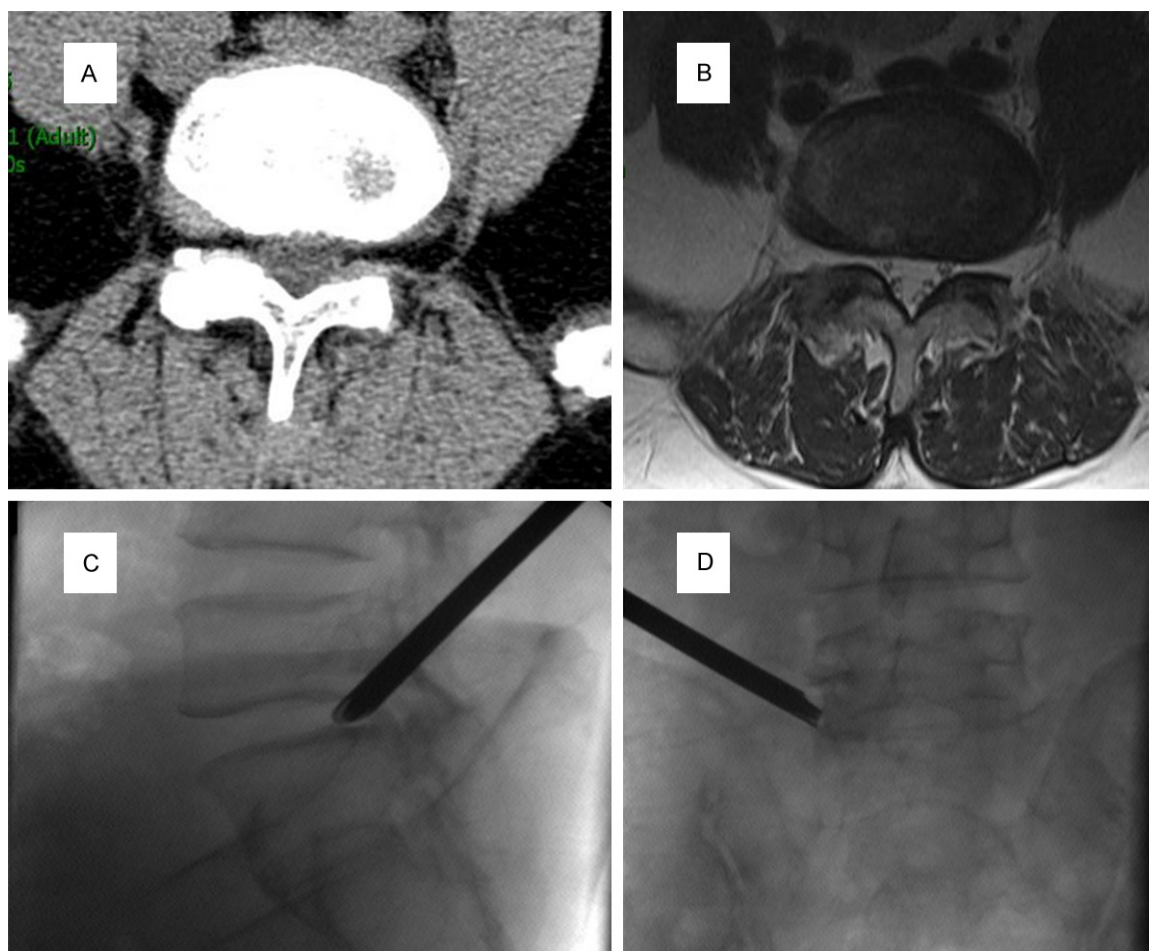


Figure 2. Preoperative PED images and radiographs of the lateral lumbar spine with position of the working catheter. A, B: Lumbar intervertebral disc CT and lumbar cross-sectional MRI suggested L5/S1 extraforaminal lumbar disc herniation; C, D: Position of working catheter.

ated with severe cardiovascular conditions, metabolic diseases or uncontrolled infections. The eligible patients and their families provided written informed contents and were free to choose either therapy after they had been fully informed of the mechanisms of actions, intraoperative end-points and potential complications of collagenase chemonucleolysis and of percutaneous endoscopic discectomy. Of 49 patients enrolled in the trial, 22 underwent PED and 27 underwent collagenase chemonucleolysis.

Surgical approaches

Preoperative preparations: Before the surgery, the locations of the herniations were confirmed based on the results of patients' lumbar disc CT and MRI, and the lateral position of lumbar spine was also marked. Prophylactic antibiotics

were administered to the patients once within 30 minutes before operation. The operations were performed on the patients under local anesthesia and placed in prone position supporting the abdomen on a pillow.

Surgical approaches: All the patients' surgeries were performed by the correspondent authors. The procedures of collagenase chemonucleolysis are as follows: under the subcutaneous anesthesia, a lateral approach to intervertebral foramen was performed using a No. 7 puncture needle to advance into the herniations with the guidance of the x-ray images [14]; 0.3 ml of iohexol (Shanghai General Electric Pharmaceutical Co., Ltd) was administered to make sure whether there was opacification of herniation at the lateral marked positions of lumbar spine (**Figure 1**). Then collagenase (Liaoning Weibang Biopharm Co., Ltd.) was injected at a

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Table 1. General information of the patients in the collagenase chemonucleolysis group and PED group

Index	Collagenase chemonucleolysis group	PED group	t/ χ^2	P value
Age	57.41±7.23	58.22±6.78	-0.406	0.687
Gender (male/female)	20/7	17/5	0.067	0.796
Segments (L2/3, L3/4, L4/5, L5/S1)	1/6/14/6	0/4/11/7	—	0.719

Table 2. Comparison of therapeutic efficacy (improved MacNab criteria) at month 6 after operation between the collagenase chemonucleolysis group and PED group

Therapeutic efficacy at 6 month after operation	Collagenase chemonucleolysis group	PED group	χ^2	P value
Excellent	17	14	—	0.944
Good	7	5		
Fair/poor	3/0	2/1		

Note: comparison by exact probability method.

dose of 150 U/0.3 ml. After the removal of the needle, a skin-closure dressing was covered on the puncture. Patients were conventionally given postoperative mannitol and dexamethasone for anti-inflammation and dehydration. They were instructed to rest in bed (mainly taking the affected-side lying position) and to move their limbs while bed rest. After at least 7 days in bed and their VAS scores reduce to 0-2, they were allowed to get up with the waist bundles and to move with some proper restrictions within one month.

Percutaneous endoscopic lumbar discectomy: The technique of nucleus pulposus resection targeted at lateral intervertebral foramen was used [6]. With the guidance of the x-ray images, a No. 18 puncture needle with 1% lidocaine was introduced into intervertebral foramen with layered anesthetize and infiltration. When the position of the needle was confirmed by the images to reach to the anterior border of intervertebral foramen, 15 ml of lidocaine at the concentration of 0.5% was intravenously injected. Then, the needle was adjusted to directly advance into the herniations. A guide wire inserted into the puncture needle was taken as the midline from which a skin incision of 7-8 mm was made on the lateral area. When the guide wire was progressively introduced into the surface of the herniation, and advanced into a working catheter (not into the intervertebral space, **Figure 2**). Under the endoscope, the

lumbar disc herniation was removed to expose the intervertebral foramen nerve root and to probe the residual herniation along the nerve root. Under the endoscope, we could see whether there was compression around the nerve root; whether the surface of the nerve root was filled with the blood vessels or whether the nerve roots were repositioned. When no bleeding was observed, the catheter could be removed. The inci-

sion was closed by a single suture and then covered by a skin-closure dressing. The next morning, when the patients got up, they were instructed to wear a waist bundle to protect the wound and they were allowed to move under proper restrictions for one month.

Patients of both groups were reviewed in our department at postoperative two weeks, three months, and six months postoperatively for assessing their pain symptoms and therapeutic efficacy.

The primary outcomes of this trial included the changes in postoperative pain, the therapeutic efficacy and the postoperative complications at six months after operation. The preoperative and intraoperative pain symptoms, and postoperative pain at two weeks, three months, and six months of the patients were assessed using the Visual Analogue Scale (VAS, 0-10; 0 stands for no pain and 10 for the worst intensity of pain). The therapeutic efficacy at 6 months after operation was evaluated using MacNab criteria (Excellent: no pain, no restriction of motility, return to normal work and level of activity; good: occasional nonradicular pain, relief of presenting symptoms, able to return to modified work and level of activity; fair: some improved functional capacity, still handicapped and/or unemployed; poor: continued objective symptoms of root involvement, additional operative of the length of postoperative follow up).

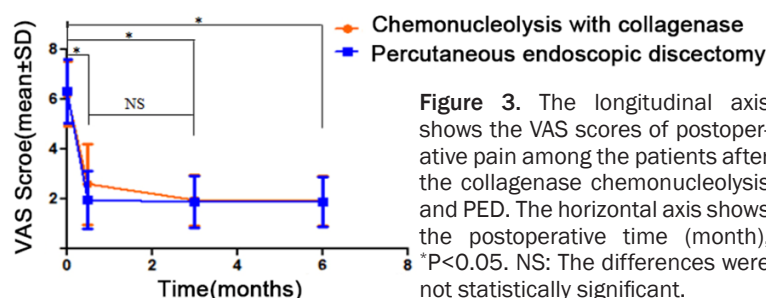


Figure 3. The longitudinal axis shows the VAS scores of postoperative pain among the patients after the collagenase chemonucleolysis and PED. The horizontal axis shows the postoperative time (month), * $P < 0.05$. NS: The differences were not statistically significant.

Additional outcomes included operation duration, postoperative bedtime duration and hospitalization costs.

Statistical analysis

Data analysis was performed using SPSS19.0 statistical processing software. VAS scores at various time points were detected using repeatedly measured and designed analysis of variance; the significance level was compared and adjusted between groups. Other measurement data across groups were compared using the t test and rank sum test. The chi square test or exact probability method was used to compare the quantitative data. The significance level was presented as 0.05 (bilaterally).

Results

The basic information was similar among the patients in both groups and the differences in age, sex, and the herniated segments were of no statistical significance (**Table 1**, $P > 0.05$). The therapeutic efficacy at six months after operation was similar among the patients in both groups (improved MacNab criteria, **Table 2**).

The results of repeatedly measured and designed analysis of variance show that the postoperative VAS scores at 2 weeks, 3 months and 6 months were significantly different from the preoperative VAS scores in the collagenase chemonucleolysis group ($P < 0.05$), and such differences were also found in the PED group. However, there were no significant differences in postoperative pain VAS scores between the collagenase chemonucleolysis group and the PED group ($P = 0.506$, **Figure 3**).

The differences between the collagenase chemonucleolysis group and the PED group were statistically significant in hospitalization costs,

operation duration, bed rest duration and intraoperative pain scores (**Table 3**, $P < 0.05$). Compared with the PED group, the collagenase chemonucleolysis group had longer bed rest duration but reduced hospitalization costs, operation duration, and intraoperative pain scores. Among all the patients in the PED group,

one gave up the surgery due to intolerance to the pain; another received postoperative meclizine, gabapentin and epidural nerve block therapy as causalgia occurred in primary pain area after the PED operation, and the symptoms were relieved at six weeks. Meanwhile, one patient with collagenase chemonucleolysis manifested worse pain complicating with numbness in the innervation area when getting up independently at 5 days after operation. The lumbar MRI review of that patient showed swollen lumbar disc herniation and increased T2 image signal (**Figure 4**), and immediate relief of pain occurred after the epidural nerve block therapy. Both groups of patients did not present any injury in motor nerves, infections and other severe complications.

Discussion

Lumbar disc herniation is a common clinical disease. Herniations may stimulate nerve roots by direct compressing nerve roots or by secondary inflammatory mediators, leading to root pain [15]. Extraforaminal lumbar disc herniation is a special subtype of lumbar disc herniation. Compared with other types of herniations, it is more likely to cause severe root pain and nerve injuries in various degrees [3]. PED and collagenase chemonucleolysis are more advantageous over open surgery in its local anesthesia and reduced muscular injuries in the articular processes and in the lumbar-sacral region [6, 16]. However, few studies have been involved in the comparison of advantages and disadvantages of collagenase chemonucleolysis and of percutaneous endoscopic discectomy (PED).

PED, detecting herniations compressing the nerve roots under endoscopy, can quickly relieve radicular pain [6]. Insertion of guide catheter or working catheter, intraoperative working

Table 3. Comparison of general hospitalization indexes and postoperative complications between collagenase chemonucleolysis group and PED group

Index	Collagenase chemonucleolysis group (n=27)	PED group (n=22)	t/Z/ χ^2	P value
Hospitalization cost	0.97±0.12	2.35±0.17	-33.25	P<0.001
Operation duration	20.4±3.7	73.7±10.2	-25.24	P<0.001
Bed rest duration	9.74±2.65	1.00±0.00	Z=-6.19	P<0.001
Intraoperative pain scoring	2.56±1.60	5.95±1.62	-7.34	P<0.001
New numbness or deteriorated numbness	1	3	4.083	P=0.159
Causalgia	0	1	—	P=0.449*
Decreased muscular strength	0	0	0	P=1
Failed operation	0	1	—	P=0.449*

Note: *Comparison by exact probability method.

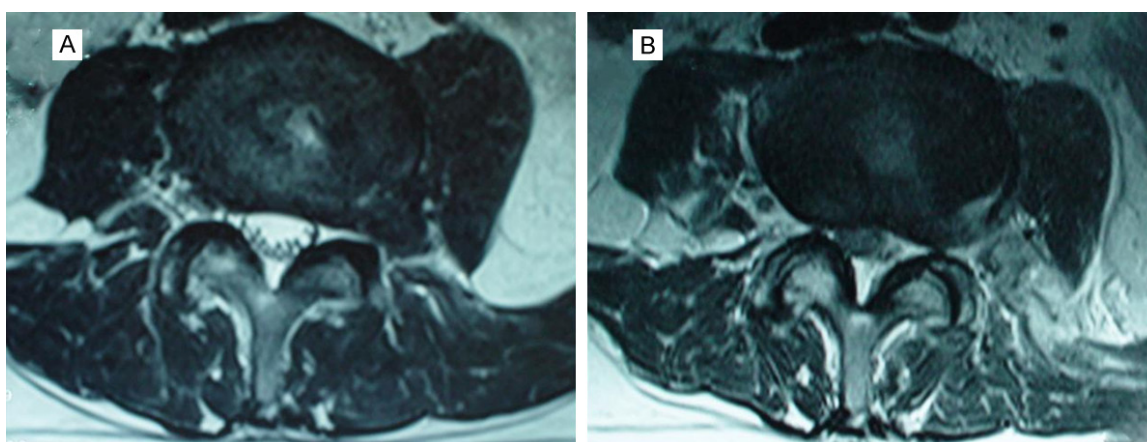


Figure 4. MRI cross-sectional images before and after collagenase chemonucleolysis. A: Preoperative cross-sectional image of herniation (T2 image) with extraforaminal lumbar disc herniation; B: Postoperative cross-sectional image of herniation (T2 image): herniation is bigger than before. T2 image shows higher signal intensity.

catheter swing, radio frequency (RF) laser applications, perfusion fluid pressure and other stimulating factors, may directly provoke nerve roots, inducing severe pain [7]. Intraoperative pain not only increases the patient's pain, but also interferes with the doctor's operation. Choi et al. suggested the injection of enough local anesthetics into the intervertebral foramen could relieve intraoperative pain [6]. We administered 15 ml of 0.5% lidocaine to the patients, but they still suffered moderate to severe pain during surgery. Among them, one withdrew from the surgery due to the intolerable pain. Zheng et al. also reported two patients withdrew from the surgery due to the intolerable pain during the treatment of far lateral disc herniations by PED [7]. Epidural space injection of local anesthetics at low concentrations could

relieve intraoperative pain in the treatment of extraforaminal lumbar disc herniation according to Guo et al. [17]. The drugs injected in the intervertebral foramen could diffuse to the epidural space (**Figure 5**), achieving the effect of epidural block. This suggests the intraoperative pain of PED is related to the shape of the targeted herniations. Secondary nerve root inflammation which may be caused by compression of extraforaminal disc herniation on roots or dorsal root ganglion may lead to increased sensitivity of nerve root [3]. In the course of PED, herniations and nerve roots at the outlet are required to be exposed under the endoscope, the extraforaminal lumbar nerve roots are likely to be irritated and lead to severe pain as they are constrained by pedicle or foramina ligaments. However, the collagenase chemonucle-

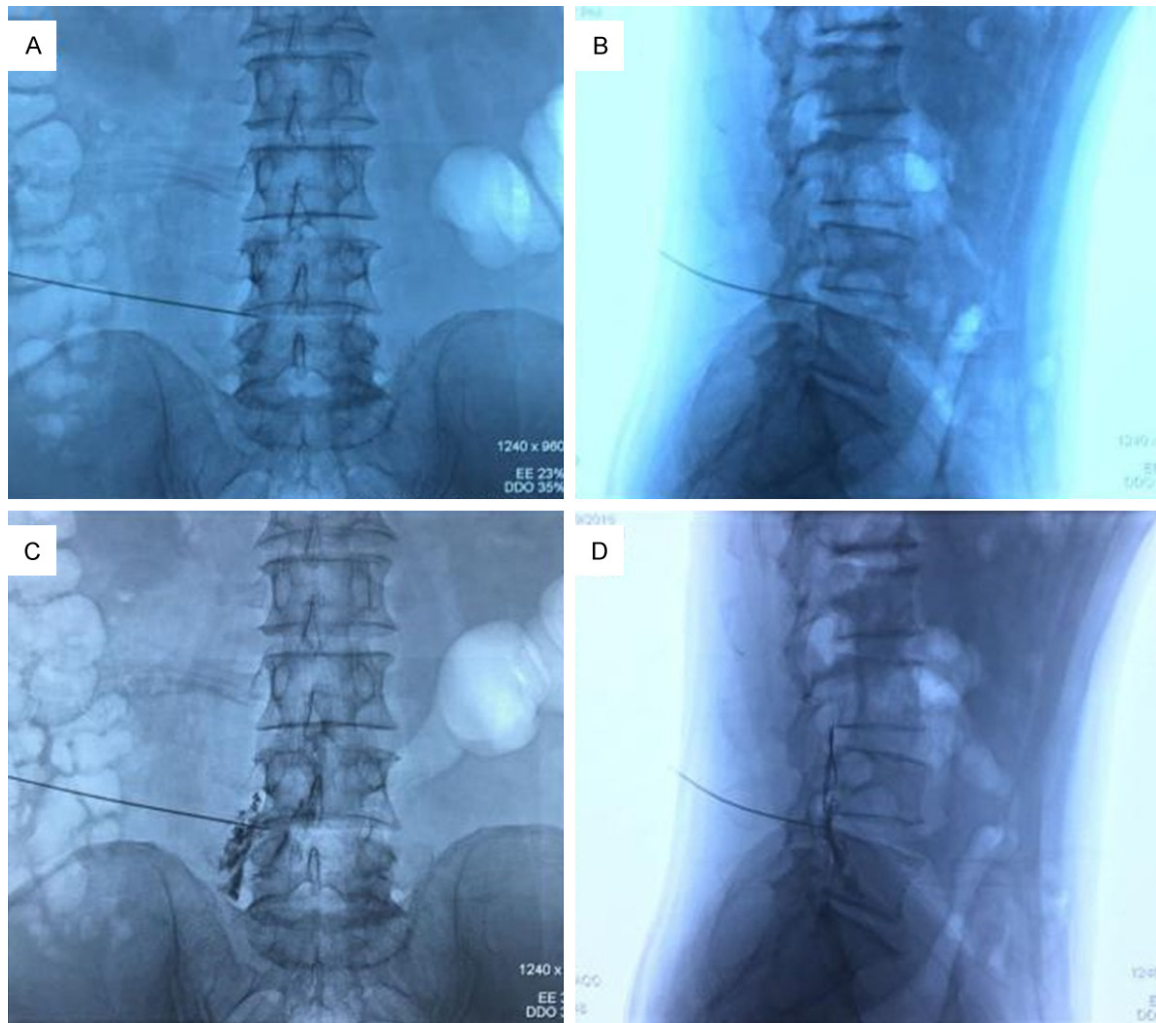


Figure 5. Radiographs of the lateral lumbar spine with position of needle tip and dispersion of contrast agents shot when local anesthetic injected in intervertebral foramen in percutaneous endoscopic discectomy. A, B: Needle tip lies in anterior edge of intervertebral foramen; C and D: Contrast agents revealed opacification intra- and extra-vertebral foramen and in ventral epidural space.

olysis therapy may not induce obvious intraoperative pain as it does not need to expose or directly provoke nerve roots.

Collagenase can specifically hydrolyze collagen in three-dimensional helical structure [18]. After collagenase is injected into the lumbar disc and collagen is hydrolyzed, proteoglycans are lysed without any restraint [19]. Collagen protein and proteoglycan, major constituents of the nucleus, degrade into such amino acids as proline and hydroxyproline which are neutralized and absorbed by the body, leading to the decrease or disappearance of the herniations [18]. In the present trial, the excellent rate at 6 months after surgery was 88.9%, which was similar to that of the PED. Hedtmann et al.

reported 70% of the excellent rate after collagenase had been directly injected into the center of the intervertebral discs which was consistent with our findings [20]. Zhang et al. performed a discography for the patients with extraforaminal lumbar disc herniations, contrast agents in 22% patients did not diffuse in the herniations [13]. Therefore, injecting collagenase into the control intervertebral discs may not guarantee the dispersion of collagenase solution inside the herniations, so the herniations in some patients are difficult to reduce or disappear. In the present trial, angiography was performed in the herniations. Collagenase was reinjected after the dispersion of contrast agents inside the herniations, to ensure that collagenase could fully contact with the colla-

gen within the herniations. Thus the herniations could be decreased or disappeared. Zhao et al. injected collagenase into 88 patients for the treatment of extraforaminal lumbar disc herniations after angiography. The excellent rate was 89.8% at 3 to 24 months after operation, and the size of the herniations was reduced in more than 50% patients or disappeared in 91.7% patients at 3 to 12 months after surgery [14].

The collagenase chemonucleolysis therapy is similar to the lumbar discography in the procedures of therapy, but the former has no learning curves (graphical representation of the increase of learning (vertical axis) with experience (horizontal axis)) as the PED does [21]. Clinically, much attention should be paid to preventing from any secondary pain symptoms or nerve injury after dissolution of the herniations. In our study, the postoperative pain symptoms at 2 weeks were not different from those after the PED therapy. Only one patient (3.7%) developed transient numbness, which was far lower than the 17% incidence rate of transient numbness and twelve-week postoperative pain reported by Brown et al. [22]. We concluded that the pain might be correlated with the forms of herniations, the injection dosage of collagenase, the bed rest duration as well as the anti-inflammatory and dehydration drugs administered at the earlier stage.

Collagenase may destroy collagen fiber structure of nucleus pulposus, and increase water imbibition of proteoglycan, which may lead to increased intervertebral lumbar discs pressure and swollen herniation, or secondary inflammatory responses. As a result, it may cause deterioration of lumbocrural pain or nerve injury [13, 22, 23]. Additionally, the patient's daily activities may result in further increased intervertebral disc pressure [24, 25]. Furthermore, a large dose of collagenase can dissolve the inner fibrous annulus, leading to the increasing risk for the dissolution of herniation in the intervertebral space, which may further deteriorate lumbocrural pain or nerve injury. Therefore, such methods as a decrease in the injection dose of collagenase, prolonging the bed rest duration, or earlier administration of anti-inflammatory drugs may reduce the risk of deteriorated lumbocrural pain or nerve injury [18, 23, 26, 27]. In addition, extraforaminal

lumbar disc herniations are mainly presented as sequestered herniations [28]. After the dissolution of collagen fibers, nucleus pulposus is not bound by the fibrous annulus, so all these dissolved matters may flow away from the direction of nerve roots due to gravity, which can accelerate relief in clinical symptoms.

Limitations

However, the follow-up duration in the present trial is not long enough to confirm long-term therapeutic efficacy of the two protocols. As the patients become older, the aggravation of intervertebral disc degeneration may lead to decreased intervertebral height and secondary intervertebral foramen stenosis, which may cause the recurrence of pain in radiculopathy. Therefore, additional studies are planned to investigate the long-term therapeutic efficacy of both protocols.

Conclusion

In conclusion, both collagenase chemonucleolysis and PED are effective in the treatment of extraforaminal lumbar disc herniations. Although collagenase chemonucleolysis requires longer bed rest after operation, it is more advantageous in relieving intraoperative pain, less hospitalization costs and simpler operation. Therefore, collagenase chemonucleolysis is a recommendable method for the treatment of extraforaminal lumbar disc herniation.

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Disclosure of conflict of interest

None.

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