

Short-Term Outcome and Predictors of Therapeutic Effects of Intradiscal Condoliase Injection for Patients with Lumbar Disc Herniation

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Abstract:

Introduction: Intradiscal chondroitin sulfate ABC endolyase (condoliase) injection for lumbar disc herniation (LDH) is an intermediate between conservative treatment and surgery. This approach can only be performed once in a lifetime; therefore, understanding the factors that determine the indication for the use of condoliase and predict outcomes is important. The aim of this study was to review clinical and imaging findings in patients after intradiscal condoliase injection, and to assess the short-term outcomes and factors associated with therapeutic effects.

Methods: The subjects were 42 patients with LDH who underwent intradiscal condoliase injection. Patients with and without a $\geq 50\%$ improvement from baseline of leg pain at 3 months after injection were defined as responders and non-responders, respectively. Clinical features and radiological findings were compared between these groups.

Results: Of the 42 patients, 32 (76.2%) were responders and 10 (23.8%) were non-responders. Of 8 patients with a history of discectomy at the same level as LDH, 6 (75.0%) were responders. Non-responders had a significantly longer time from onset to treatment, smaller herniated volume before treatment, lower percentage reduction of herniated mass, and less intervertebral disc degeneration before treatment. There were no significant differences in LDH types (subligamentous extrusion or transligamentous extrusion types), high-intensity area within the herniation, changes in disc height, and region of condoliase injection between the two groups.

Conclusions: Intradiscal condoliase injection had a good short-term therapeutic effect in patients with LDH, including in transligamentous extrusion-type and revision cases as well as subligamentous extrusion-type cases. Administration of intradiscal condoliase injection may be most effective in patients with a larger herniated mass volume before treatment, and least effective in cases with a longer time and less intervertebral disc degeneration before treatment.

Keywords:

chondroitin sulfate ABC, condoliase, lumbar disc herniation, outcomes, predictors, therapeutic effects

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Introduction

Lumbar disc herniation (LDH) is a common disease that involves nerve root compression by degenerated nucleus pulposus and occurs at a particularly high rate in the 20s to 40s age group. For these patients, conservative treatment is recommended, but surgery is required for cases that are refractory to prolonged conservative treatment. A prospective randomized observational 8-year cohort study suggested an ad-

vantage of surgery compared with conservative treatment¹⁾, but a longitudinal observation study of 34,639 operations found rates of 2.7% for surgical complications and 2.1% for repeat surgery within 90 days²⁾. In a 13-year follow-up study in patients with severe and persistent sciatic pain due to LDH, 8% of those treated surgically had revision surgery at the same level, and 14% of the conservatively treated cases had undergone spinal surgery³⁾.

In the American Pain Society Clinical Practice Guidelines,

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an evidence review suggested that chemonucleolysis is somewhat more effective than placebo, but that surgery is a superior treatment⁴). Chemonucleolysis is viewed as an intermediate method between conservative and surgical treatment, and use of chymopapain for this purpose was approved by the United States Food and Drug Administration in 1982; however, chymopapain was discontinued in 1999 due to protease activity and low substrate specificity disturbing nerve root and anaphylactic reactions⁵). Chondroitin sulfate ABC endolyase (condoliase) is an alternative to chymopapain for use in chemonucleolysis. Condoliase is a pure mucopolysaccharidase derived from the gram-negative rod *Proteus vulgaris*, and has no protease activity. However, condoliase has high substrate specificity for chondroitin sulfate and hyaluronic acid, which are abundant glycosaminoglycans on proteoglycans in the nucleus pulposus of intervertebral discs. Clinical trials for contained-type LDH (protrusion- and subligamentous extrusion-type LDH) at L4-5 and L5-S1 have shown the safety and efficacy of condoliase, and the drug regulatory authority in Japan has approved this protein for intradiscal treatment of LDH^{6,7}). The therapeutic effects of condoliase for uncontained-type LDH (transligamentous extrusion and sequestration type) refractory to conservative treatment required clarification, although we also note that these LDH types are likely to regress spontaneously with time⁷).

Condoliase can only be used once in a lifetime to prevent anaphylactic reactions, which makes it particularly important, especially for spine surgeons, to understand predictors of its efficacy to identify likely responders and determine the indication for the use of condoliase. The aim of this study was to review clinical and imaging findings in patients with LDH treated with intradiscal condoliase injection, and to assess the short-term outcomes and predictors of therapeutic effects.

Materials and Methods

Study population

Between May 2019 and April 2020, a total of 46 consecutive patients with LDH have undergone intradiscal condoliase injection at our two institutions. Among the 46 patients, 42 completed the minimum follow-up period of 3 months (follow-up rate: 91.3%). The study protocol was approved by the Human Ethics Review Committee of our University Medical Faculty and strictly followed the Clinical Research Guidelines of the Ministry of Health, Labor, and Welfare of the Japanese Government.

All patients had clinical signs and symptoms of LDH. The indications for intradiscal condoliase injection were symptoms of unilateral lower-extremity pain and persistent neurological signs at the level of the herniated disc on high-resolution magnetic resonance imaging (MRI) that were refractory to conservative treatment such as rest, medication (non-steroidal anti-inflammatory drugs, pregabalin, trama-

dol), and nerve root block for at least 1 month. Patients with multilevel disc herniation, motor and/or sensory disturbance, including bladder dysfunction and neurogenic intermittent claudication as a symptom of lumbar spinal canal stenosis, were excluded from the study. There were no patients with spinal instability or lateral LDH in this study population.

Outcomes and radiological measurements

Clinical and radiological assessments were conducted before and 3 months (12-14 weeks) after injection. The intensity of leg and back pain was measured using a numerical rating scale (NRS), on which 0 and 10 indicated no pain and the worst pain ever experienced, respectively. Patients with $\geq 50\%$ improvement of leg pain at 3 months after injection compared to baseline were classified as responders, and all others as non-responders^{7,8}). Clinical data for affected level, age, gender, and time from onset were acquired from medical charts. Axial and sagittal MRI were used to classify the herniation types (subligamentous extrusion and transligamentous extrusion types)⁹, the extent of intervertebral disc degeneration based on Pfirrmann classes and on a modified classification^{10,11}). The Modic approach was used to classify signal changes in vertebral bodies adjacent to cartilage endplates¹²). The presence of a high-intensity area within extruded disc herniation¹³, and the herniated disc volume (mm^3), extent of LDH, and disc height (Fig. 1) were evaluated using published methods¹⁴). Herniated disc areas were measured on sagittal sections between the lateral margins of each pedicle. On each section, reference lines were drawn between the endpoints of the posterior edges of the superior and inferior endplates. The herniated disc area (mm^2) was measured using a picture archiving and communication system, and the herniated volume (mm^3) was obtained by multiplication of the area by the scan thickness (mm) (Fig. 1C). The posterior vertebral height was divided into three equal parts. The extent of LDH defined by the most distal endpoint (or proximal in cases with upward migration) of migrated herniation was classified as none (class 1), and in the proximal one-third (class 2), middle one-third (class 3), and distal one-third (class 4) of the posterior height of the superior or inferior vertebra (Fig. 1D). Disc height was calculated at the midpoint of the vertebra on mid-sagittal MRI¹³). The condoliase injection region was assessed on frontal and oblique views on plain lumbar radiography. On each image, lines were drawn between the endpoints of the vertebral edges, and the middle one-third on both images was defined as the median injection point (Fig. 1E). All measurements were performed in triplicate by two observers and the average value was used.

Procedure

Intradiscal condoliase injection was performed under fluoroscopic guidance in a semi-lateral position. A single 1-mL dose of condoliase (1.25 U/mL) was injected toward the middle of the affected intervertebral nucleus pulposus from the non-symptom side using a 21-gauge puncture needle^{6,7}).

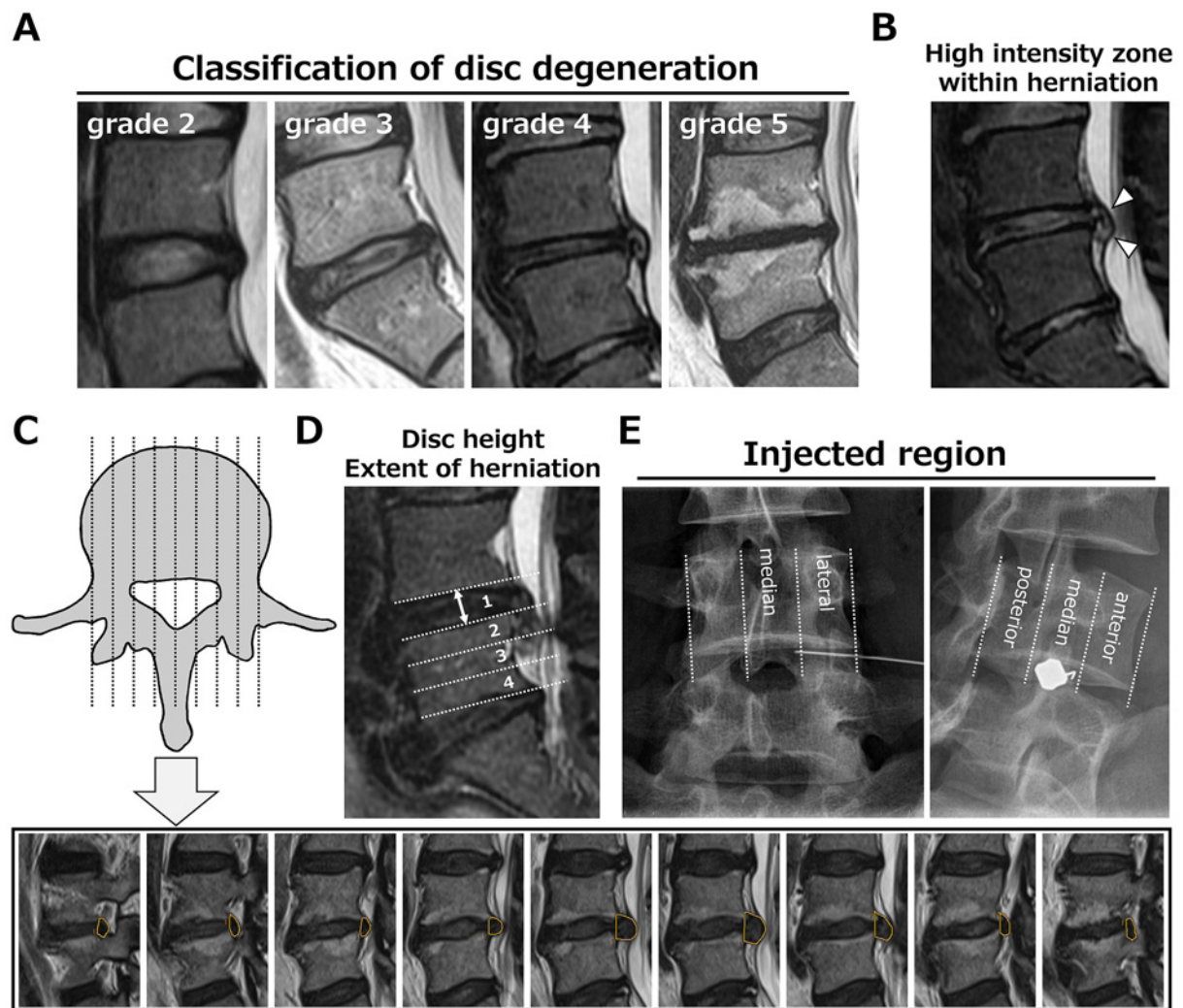


Figure 1. Radiological assessments. (A) Degree of disc degeneration using the Pfirrmann classification. (B) Occurrence of a high-intensity area within the herniation. (C) Measurements of herniated mass volume. (D) Disc height and extent of herniated mass. (E) Region of condoliase injection.

Injections were performed under local anesthesia by spine surgeons who were board-certified and familiar with intradiscal injection. Patients were closely observed for 2 hours after injection for appearance of anaphylactic reactions.

Statistical analysis

Data are shown as mean±SD. Intergroup differences were examined by Wilcoxon signed-rank test, Mann-Whitney *U* test or chi-square test, with *p*<0.05 considered to be significant. Inter- and intraobserver reliability were assessed using intraclass correlation coefficients. All analyses were conducted using SPSS (version 24.0, SPSS, Chicago, IL, USA).

Results

Clinical data

A total of 42 patients (29 males, 13 females) with LDH who underwent intradiscal condoliase injection were enrolled in the study. A summary of the clinical data of the

patients is shown in Table 1. The mean age at baseline was 46.0±13.8 years. Eight patients had prior discectomy at the same level as LDH. The affected intervertebral discs were L 2-3 (n=2, 4.8%), L3-4 (n=2, 4.8%), L4-5 (n=23, 54.8%), and L5-S1 (n=15, 35.7%). Of the 42 patients, 32 (76.2%) were defined as responders (≥50% improvement in leg pain) and 10 (23.8%) as non-responders (<50% improvement). No severe adverse effects such as anaphylactic reactions occurred, although a temporary increase in low back pain after treatment was observed in 5 cases (11.9%). A change in Modic class occurred in 2 cases (4.8%) after treatment, and the increased low back pain was not associated with this change.

Mean age, gender, NRS (leg pain and back pain), and follow-up periods did not differ significantly between responders and non-responders at the time of injection. However, patients in their 20s were significantly more frequently non-responders (3/10 [30.0%] vs. 2/32 [6.3%], *p*=0.043), and the time from onset to treatment was significantly longer in non-responders (74.9 vs. 31.7 weeks, *p*=0.021). Of

Table 1. Comparison of Clinical Data at Baseline for Responders and Non-Responders.

| Parameter | Responders | Non-responders | p |
|--|-------------------|--------------------|--------|
| Case number (%) | 32 (76.2%) | 10 (23.8%) | |
| Affected levels | | | |
| L2-3 | 2 (6.3%) | 0 | 0.40 |
| L3-4 | 2 (6.3%) | 0 | |
| L4-5 | 15 (46.9%) | 8 (80.0%) | |
| L5/S1 | 13 (40.6%) | 2 (20.0%) | |
| Age (years) | 47.7±13.2 | 41.0±14.7 | 0.22 |
| Gender (male, female) | 23, 9 | 6, 4 | 0.48 |
| Time from onset (range) (weeks) | 31.7±39.8 (4–180) | 74.9±46.9 (11–148) | 0.021* |
| NRS before treatment | | | |
| leg pain | 6.7±1.7 | 7.3±2.1 | 0.38 |
| back pain | 3.8±2.6 | 4.6±2.6 | 0.40 |
| Prior discectomy at the same level | 6 (75.0%) | 2 (25.0%) | 0.93 |
| Follow-up period (weeks after injection) | 12.8±0.9 | 12.9±1.0 | 0.88 |

NRS: numerical rating scale

*p<0.05

Table 2. Comparison of Radiological Data for Responders and Non-Responders.

| Parameter | Responders (n=32) | Non-responders (n=10) | p |
|---|-------------------|-----------------------|----------|
| Classifications of herniation | | | |
| subligamentous extrusion | 14 (43.8%) | 6 (60.0%) | 0.37 |
| transligamentous extrusion | 18 (56.3%) | 4 (40.0%) | |
| High signal intensity area within herniation | 14 (43.8%) | 4 (40.0%) | 0.83 |
| Herniated mass volume before treatment (mm ³) (all cases) | 1426.3±645.1 | 1045.0±319.2 | 0.035* |
| (cases with subligamentous extrusion-type herniation) | (1300.4±718.1) | (927.1±228.6) | (0.12) |
| (cases with transligamentous extrusion-type herniation) | (1512.5±618.2) | (1221.9±386.1) | (0.27) |
| Reduction rate of herniated mass volume (%) (all cases) | 34.4±19.3 | 9.9±3.4 | <0.01* |
| (cases with subligamentous extrusion-type herniation) | (30.4±20.1) | (10.5±7.5) | (<0.01*) |
| (cases with transligamentous extrusion-type herniation) | (35.7±19.1) | (9.1±16.9) | (<0.01*) |
| Change in disc height (mm) | 1.3±0.6 | 1.7±0.6 | 0.11 |
| Pfirrmann grade before treatment | | | |
| (grades 2 and 3) | 16 (1–15) | 9 (4–5) | 0.025 * |
| (grades 4 and 5) | 16 (15–1) | 1 (0–1) | |
| Injected region (outside median) | 3 (9.4%) | 2 (20.0%) | 0.37 |

*p<0.05

the 32 responders, 21 (65.6%) received condoliase injection within 6 months from onset, whereas only 2 in 10 non-responders (20.0%) received condoliase injection within this period. Interestingly, of 8 patients with a history of discectomy at the same level, 6 (75.0%) were responders, and there was no difference in efficacy between the initial and revision cases (p=0.93).

Radiological data

A summary of differences in radiological data for responders and non-responders is shown in Table 2. There were no significant differences in the classifications of herniation (subligamentous extrusion or transligamentous extrusion-type, p=0.37), rate of a high signal intensity area within the herniation (43.8% vs. 40.0%, p=0.83), or changes in disc height (1.3 vs. 1.7 mm, p=0.11). However, the herniated mass volume before treatment (1426.3 vs. 1045.0 mm³, p=0.035) and the percentage reduction of the herniated mass volume after treatment (34.4% vs. 9.9%, p<0.01) were significantly higher in responders. Interestingly, condoliase was

significantly less effective in Pfirrmann grades 2 and 3 cases before injection (remaining signal intensity zone in the intervertebral disc) than in those in Pfirrmann grades 4 and 5 (moderate or severe intervertebral disc degeneration; p=0.025)⁹). Efficacy was not associated with the site of the injection relative to the defined median position. The difference in the extent of disc herniation before and after intradiscal condoliase injection is shown in Table 3. All cases in classes 3 or 4 (all cases with transligamentous extrusion-type LDH) before treatment were in class 1 or 2 after treatment. The inter- and intraobserver reliabilities for imaging findings were both excellent (p>0.75).

Representative cases

Results for two patients who underwent intradiscal condoliase injection for LDH refractory to conservative treatment are shown in Fig. 2. A 51-year-old female (Fig. 2A) with L4-5 LDH had experienced left lower-extremity pain for 17 weeks. The NRS for leg pain and back pain improved from 8 and 5 at baseline to 1 and 2 at 3 months af-

ter treatment. On MRI, distally migrated herniation (Pfirrmann grade 4 [moderate degeneration]; no high signal intensity area within the herniation; disc height, 10.7 mm; extent of LDH, class 3 (transligamentous extrusion-type); herniated mass volume, 1917.0 mm³) was reduced 3 months after injection (Pfirrmann grade 4; disc height, 8.6 mm; disc extent, class 2; herniated mass volume, 994.1 mm³, reduction rate, 48.1%). A 21-year-old male (Fig. 2B) with L4-5 LDH had experienced left lower-extremity pain for 78

weeks. The NRS for leg pain and back pain changed from 9 and 5 at baseline to 5 and 3 at 3 months after treatment, indicating limited efficacy. On MRI, the LDH (Pfirrmann grade 3 [mild degeneration]; high signal intensity area within the herniation; disc height, 9.8 mm; extent of LDH, class 1 [subligamentous extrusion-type]; herniated mass volume, 777.9 mm³) was only slightly reduced 3 months after injection (Pfirrmann grade 4; disc height, 8.9 mm; disc extent, class 1; herniated mass volume, 755.4 mm³, reduction rate, 10.0%).

Table 3. Difference in Extent of Disc Herniation before and after Intradiscal Condoliase Injection.

| | Extent of LDH 3 months after injection | | |
|--------------------------------|---|---------|-------|
| | Class 1 | Class 2 | |
| Extent of LDH before injection | Class 1 | 17 [6] | 0 |
| (Total number [Non-responder]) | Class 2 | 7 | 8 [4] |
| | Class 3 [†] | 6 | 2 |
| | Class 4 [†] | 0 | 2 |

[†]Classes 3 and 4: all cases were transligamentous extrusion-type herniations.
LDH: lumbar disc herniation

Discussion

The aim of this study was to assess short-term outcomes and predictors of therapeutic effects of intradiscal condoliase injection. Significant efficacy by 3 months after treatment was obtained in 76.2% of the patients, which suggests that this injection is effective as an option to surgery for cases refractory to conservative treatment. In addition, NRS scores in 6 of 8 revision cases (75.0%) were also significantly improved. The key predictors of therapeutic effects were as follows: 1) positive impact of a larger herniated mass vol-

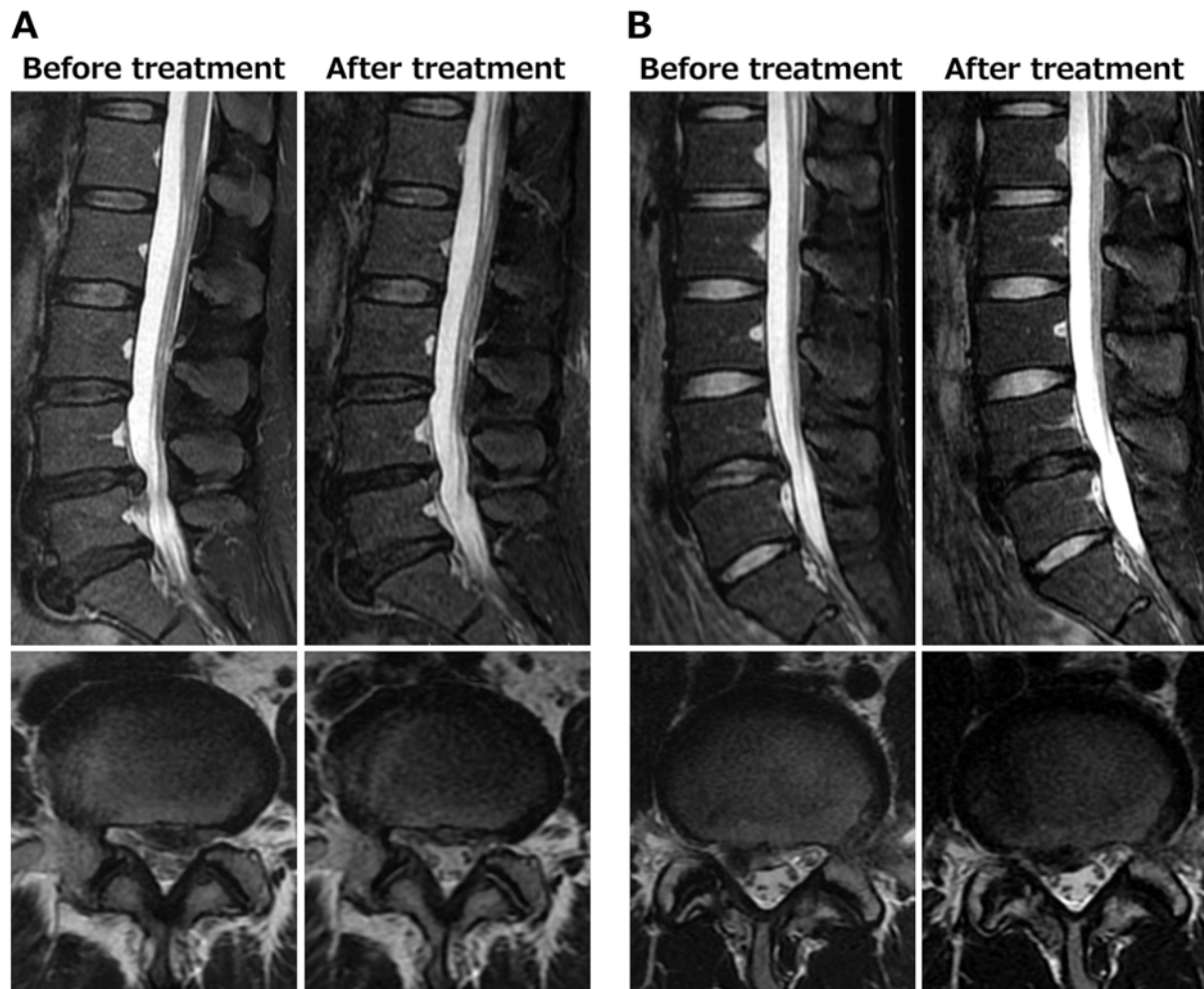


Figure 2. Representative cases. (A) L4-5 LDH in a 51-year-old patient: Pfirrmann grade 4; disc extent class 3 was reduced to grade 4; class 2 (reduction rate 48.1%). (B) L4-5 LDH in a 21-year-old patient: Pfirrmann grade 3 was not reduced (grade 4; reduction rate 10.0%). LDH: lumbar disc herniation

ume, even for distally migrated herniation (class 3 or 4 including transligamentous extrusion-type), and 2) negative impacts of a longer time and lower intervertebral disc degeneration (remaining high-intensity zone in the intervertebral disc) before treatment.

The timing of the indication for condoliase treatment is an important clinical question. Some prospective studies have suggested that pain lasting more than 6-12 months correlates with an unfavorable postoperative outcome¹⁵⁻¹⁸, but other reports have found spontaneous regression of LDH at rates of 45.5% at 3 months¹⁹ and >60% at 6 months²⁰ after presentation, especially in patients with extrusion- and sequestration-type LDH. In our study, the period before treatment was significantly longer in non-responders compared with responders (74.9 vs. 31.7 weeks), and the percentages of patients who received condoliase injection within 6 months from onset were 65.6% in responders and 20.0% in non-responders. Previous studies on the natural history of LDH have shown that sciatic pain improved in 70% of patients at 4 weeks after presentation²¹, and at 2.9 months in patients with extrusion-type LDH²². From these findings, we suggest that intradiscal condoliase injection should be performed ≤ 6 months from disease onset.

Identification of negative predictors of the efficacy of intradiscal condoliase treatment is also important clinically, despite the positive efficacy in 76.2% of our patients. The initial herniated mass volume and the percentage reduction of this volume after treatment were significantly larger in responders, which is consistent with previous reports showing an association between spontaneous regression of LDH and pain relief. The safety and efficacy of condoliase have been confirmed only for patients with subligamentous extrusion-type LDH in clinical trials in Japan, given the risk of condoliase not reaching its target and cause anaphylactic reactions, but regression of the herniated mass was found even in LDH extended to the middle (class 3) or distal (class 4) one-third of the posterior vertebral height, including transligamentous extrusion-type LDH. Thus, a larger herniated mass might have a positive impact on intradiscal condoliase treatment. On the contrary, a smaller degree of extrusion of LDH might be negative. MRI has been shown to predict classifications of LDH with an accuracy of 80.6%²³, but the important point for indication of condoliase might be the visualized herniated mass volume before treatment rather than the classification of herniation.

A negative effect of less intradiscal disc degeneration was also suggested in the current study. Condoliase dehydrates glycosaminoglycans (mainly chondroitin sulfate) on proteoglycans that are abundant in the nucleus pulposus of the intervertebral disc. Theoretically, the mucopolysaccharidase effect should occur more in patients with less intervertebral disc degeneration. On the other hand, this action may depend on the initial distribution of condoliase in the disc and the degree of fibrosis of the nucleus. Patients with less degenerated discs may require greater injection pressure and be less extensible than those with degenerated discs. In this

study, progression of Pfirrmann grade occurred in 11 (44.0%) of 25 cases in grade 2 or 3, while better therapeutic effects of condoliase occurred in patients with advanced degeneration of Pfirrmann grades 4 and 5. Interestingly, a similar positive efficacy was observed in patients with revision LDH, despite greater fibrosis of the nucleus after nucleotomy. These results did not depend on the injected region, which suggests that the efficacy of intradiscal condoliase injection may be influenced by the degree of posterior annulus rupture and the distribution of condoliase, rather than the extent of intervertebral disc degeneration. Careful consideration of treatment with condoliase injection is required for patients with less degenerated discs, as well as those with severely degenerated discs containing little proteoglycan in the nucleus pulposus.

The most important factor in determining the therapeutic effect might be how much condoliase acts on LDH. A recent retrospective study showed an association between a high-intensity area within the herniation on T2-weighted MRI, indicating hydrated LDH, and increased efficacy of condoliase due to induction of dehydration of the nucleus pulposus¹³. However, a high-intensity area was not significant in the current study, with rates for this area of 43.8% in responders and 40.0% in non-responders. Some clinical studies have suggested an association between a high-intensity area within the herniation and low back pain^{24,25}, younger age, and shorter duration of radicular pain²⁶. On the other hand, a recent review of population-based studies found conflicting results for the prevalence (14%-63%) of a high-intensity area and its correlation with low back pain²⁷. Based on our results, a finding of a high-intensity area within an extruded herniation on MRI before treatment might not be a positive indicator for the therapeutic effects of condoliase.

This study has certain limitations. First, it was a retrospective, short-term follow-up study that included only 42 patients and did not include a statistical power analysis. Larger scale population studies are needed to provide further evidence to validate our findings. Second, it is not possible to distinguish with certainty whether the positive therapeutic effect was due to intradiscal condoliase treatment or the natural history of LDH. Third, although the short-term therapeutic effect was sufficient, the long-term clinical outcome and adverse effects are uncertain. In a 10-year matched cohort study, disc puncture and pressurized injection were found to increase the risk of clinical disc problems requiring lumbar surgery, new imaging findings, and prolonged back pain²⁸, although another prospective study suggested no acceleration of intervertebral disc degeneration in young patients after a 5-year follow-up²⁹. Therefore, further evaluation is needed, especially in patients with advanced intervertebral disc degeneration on MRI. Despite these limitations, we believe that our findings provide important insights and guidance on therapeutic management of intradiscal condoliase injection for patients with LDH.

In conclusion, intradiscal condoliase injection showed

good short-term therapeutic effects in patients with LDH, including transligamentous extrusion-type herniation and revision cases. However, careful consideration is required to determine whether this injection should be given to patients with a longer pain duration, smaller herniated mass volume, and lower intervertebral disc degeneration before treatment, based on our data showing that these were negative predictors for the therapeutic effect, in addition to the uncertain long-term clinical outcome.

Disclaimer: Hideaki Nakajima is one of the Editors of Spine Surgery and Related Research and on the journal's Editorial Committee. He was not involved in the editorial evaluation or decision to accept this article for publication at all.

Conflicts of Interest: The authors declare that there are no relevant conflicts of interest.

Author Contributions: Hideaki Nakajima: conception and design various aspects of the study, acquisition of patients, analysis and interpretation of data, drafting of the manuscript; Arisa Kubota: analysis and interpretation of data, statistical analysis; Yasuhisa Maezawa: conception and design of the study, acquisition of patients; Shuji Watanabe: analysis and interpretation of data, statistical analysis; Kazuya Honjoh: analysis and interpretation of data, statistical analysis; Hironori Ohmori: conception and design of the study, critical revision of the manuscript for important intellectual content; Akihiko Matsumine: conception and design of the study, critical revision of the manuscript for important intellectual content. All authors participated in the preparation of the manuscript and approved the final version.

Ethical Approval: The study protocol was approved by the Human Ethics Review Committee of Fukui University Medical Faculty (Approval Number 2014046).

References

- Lurie JD, Tosteson TD, Tosteson AN, et al. Surgical versus nonoperative treatment for lumbar disc herniation: eight-year results for the spine patient outcomes research trial. *Spine (Phila Pa 1976)*. 2014;39(1):3-16.
- Fjeld OR, Grøvlø L, Helgeland J, et al. Complications, reoperations, readmissions, and length of hospital stay in 34 639 surgical cases of lumbar disc herniation. *Bone Joint J*. 2019;101-B(4):470-7.
- Nykvist F, Hurme M, Alaranta H, et al. Severe Sciatica: A 13-year Follow-Up of 342 Patients. *Eur Spine J*. 1995;4(6):335-8.
- Chou R, Loeser JD, Owens DK, et al. American Pain Society Low Back Pain Guideline Panel. Interventional therapies, surgery, and interdisciplinary rehabilitation for low back pain: an evidence-based clinical practice guideline from the American Pain Society. *Spine (Phila Pa 1976)*. 2009;34(10):1066-77.
- Agre K, Wilson RR, Brim M, et al. Chymodiactin Postmarketing Surveillance. Demographic and Adverse Experience Data in 29,075 Patients. *Spine (Phila Pa 1976)*. 1984;9(5):479-85.
- Matsuyama Y, Chiba K, Iwata H, et al. A multicenter, randomized, double-blind, dose-finding study of condoliase in patients with lumbar disc herniation. *J Neurosurg Spine*. 2018;28(5):499-511.
- Chiba K, Matsuyama Y, Seo T, et al. Condoliase for the treatment of lumbar disc herniation: A randomized controlled trial. *Spine (Phila Pa 1976)*. 2018;43(15):E869-76.
- Dworkin RH, Turk DC, Wyrwich KW, et al. Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *J Pain*. 2008;9(2):105-21.
- Wong DA, Transfeldt E. *Macnab's Backache*. 4th ed. Philadelphia: Lippincott Williams and Wilkins; 2007. p. 77-83, 254-62.
- Pfarrmann CW, Metzdorf A, Elfering A, et al. Effect of aging and degeneration on disc volume and shape: A quantitative study in asymptomatic volunteers. *J Orthop Res*. 2006;24(5):1086-94.
- Pfarrmann CW, Metzdorf A, Zanetti M, et al. Magnetic resonance classification of lumbar intervertebral disc degeneration. *Spine (Phila Pa 1976)*. 2001;26(17):1873-8.
- Modic MT, Steinberg PM, Ross JS, et al. Degenerative disk disease: assessment of changes in vertebral body marrow with MR imaging. *Radiology*. 1988;166(1 Pt 1):193-9.
- Banno T, Hasegawa T, Yamato Y, et al. Clinical outcome of condoliase injection treatment for lumbar disc herniation: Indications for condoliase therapy. *J Orthop Sci in press*. doi: 10.1016/j.jos.2020.02.002
- Seo JY, Roh YH, Kim YH, et al. Three-dimensional analysis of volumetric changes in herniated discs of the lumbar spine: does spontaneous resorption of herniated discs always occur? *Eur Spine J*. 2016;25(5):1393-402.
- Nygaard OP, Kloster R, Solberg T. Duration of leg pain as a predictor of outcome after surgery for lumbar disc herniation: a prospective cohort study with 1-year follow up. *J Neurosurg*. 2000;92 (2 Suppl):131-4.
- Jansson KA, Németh G, Granath F, et al. Health-related Quality of Life in Patients Before and After Surgery for a Herniated Lumbar Disc. *J Bone Joint Surg Br*. 2005;87(7):959-64.
- Ng LC, Sell P. Predictive value of the duration of sciatica for lumbar discectomy. A prospective cohort study. *J Bone Joint Surg Br*. 2004;86(4):546-9.
- Rihn JA, Hilibrand AS, Radcliff K, et al. Duration of symptoms resulting from lumbar disc herniation: effect on treatment outcomes: analysis of the Spine Patient Outcomes Research Trial (SPORT). *J Bone Joint Surg Am*. 2011;93(20):1906-14.
- Komori H, Shinomiya K, Nakai O, et al. The natural history of herniated nucleus pulposus with radiculopathy. *Spine (Phila Pa 1976)*. 1996;21(2):225-9.
- Modic MT, Ross JS, Obuchowski NA, et al. Contrast-enhanced MR imaging in acute lumbar radiculopathy: a pilot study of the natural history. *Radiology*. 1995;195(2):429-35.
- Weber H. Lumbar disc herniation. A controlled, prospective study with ten years of observation. *Spine (Phila Pa 1976)*. 1983;8(2): 131-40.
- Saal JA, Saal JS. Nonoperative treatment of herniated lumbar intervertebral disc with radiculopathy. An outcome study. *Spine (Phila Pa 1976)*. 1989;14(4):431-7.
- Kim KY, Kim YT, Lee CS, et al. MRI classification of lumbar herniated intervertebral disc. *Orthopedics*. 1992;15(4):493-7.
- Carragee EJ, Paragioudakis SJ, Khurana S. 2000 Volvo Award winner in clinical studies: Lumbar high-intensity zone and discography in subjects without low back problems. *Spine (Phila Pa 1976)*. 2000;25(23):2987-92.
- Chen JY, Ding Y, Lv RY, et al. Correlation between MR imaging and discography with provocative concordant pain in patients with low back pain. *Clin J Pain*. 2011;27(2):125-30.

26. Rasekhi A, Babaahmadi A, Assadsangabi R, et al. Clinical manifestations and MRI findings of patients with hydrated and dehydrated lumbar disc herniation. *Acad Radiol.* 2006;13(12):1485-9.
27. Cheung JPY, Luk KDK. The relevance of high-intensity zones in degenerative disc disease. *Int Orthop.* 2019;43(4):861-7.
28. Cuellar JM, Stauff MP, Herzog RJ, et al. Does provocative discography cause clinically important injury to the lumbar intervertebral disc? A 10-year matched cohort study. *Spine J* 2016;16(3):273-80.
29. Ohtori S, Inoue G, Orita S, et al. No acceleration of intervertebral disc degeneration after a single injection of bupivacaine in young age group with follow-up of 5 years. *Asian Spine J.* 2013;7(3): 212-7.

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