Efficacy of Chemonucleolysis with Condoliase in Patients Aged under 20 Years

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Abstract:

Introduction: Chemonucleolysis with condoliase is a minimally invasive treatment option for lumbar disk herniation (LDH). However, studies reporting the efficacy of condoliase in patients aged <20 years are scarce. Therefore, the present study aimed to evaluate the efficacy of condoliase therapy for LDH in the aforementioned population.

Methods: Condoliase administration was determined based on adequate informed consent. The study enrolled 138 patients (mean age, 41.3±15.4 years) with LDH who received condoliase injections with a follow-up period of 1 year. The patients were divided into Group Y (age, <20 years) and Group A (age, 20-70 years). The clinical outcomes were visual analog scale (VAS) scores for leg and back pain and Oswestry Disability Index (ODI) values. Changes in disk height and degeneration were evaluated. These data were obtained at baseline and at the 3-month and 1-year follow-ups. Condoliase therapy was considered to be effective if it improved the VAS score for leg pain by ≥50% at 1 year from baseline and prevented surgery.

Results: Groups Y and A consisted of 15 and 123 patients, respectively. Condoliase therapy was effective in 9 patients (60.0%) in Group Y and 96 patients (78.0%) in Group A. The rates of Pfirrmann grade deterioration and recovery were substantially higher in Group Y than in Group A (83.3% vs. 45.8% and 50.0% vs. 16.3%, respectively). While the disk height reduction in Group Y was greater at 3 months, it recovered to the same level as that in Group A at 1 year. In Group Y, patients who did not respond to the treatment exhibited a considerably higher preoperative ODI (P<0.05).

Conclusions: Chemonucleolysis with condoliase is considered to have limited efficacy in patients aged <20 years. Caution should be taken when managing cases showing lumbar instability or existing disability. While chemonucleolysis with condoliase is a less invasive treatment option for LDH, the administration should be decided upon with sufficient consent considering the potential limited efficacy and disk degeneration.

Keywords:

chemonucleolysis, condoliase therapy, lumbar disk herniation, young

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Introduction

Chemonucleolysis, which involves chemical dissolution of the nucleus pulposus of the intervertebral disk, is a less invasive treatment option and is considered to be an intermediate treatment between conservative and surgical approaches for lumbar disk herniation (LDH)[1-3]. Contrary to chymopapain, condoliase promotes chemonucleolysis of the nucleus pulposus while causing minimal harm to the surrounding tissues owing to its lack of protease activity[4-6]. After obtaining approval in Japan in 2018 based on the results of phase III clinical trials, condoliase is now widely used in clinical practice[7,8]. Condoliase therapy exhibits high efficacy in alleviating LDH symptoms, achieving success rates of 62% to 87% with no remarkable adverse events[9-18]. Although several factors can influence the outcomes of condoliase therapy, the patient characteristics that may play a role in pain relief remain unclear[9,10,12-18].

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Condoliase is recommended for use in patients with LDH aged 20-70 years as the clinical trial included patients within this age range[7,8]. According to the appropriate use criteria, administration to patients aged <20 years should be performed with caution because of concerns regarding the impact of this treatment on growth plates. However, in cases that are resistant to conservative treatment, many patients and their parents prefer this less invasive treatment over surgery. Thus, the safety and efficacy of condoliase therapy in patients aged <20 years equivalent to those in older patients can prove to be the clinically significant.

Although condoliase therapy has demonstrated high efficacy in numerous previous studies[9-18], studies describing its efficacy in patients aged <20 years are scarce. Furthermore, although Oshita et al.[17] showed that condoliase therapy was effective in three out of four patients aged <20 years, its efficacy in those aged <20 years remains unclear due to the limited number of cases. Kobayashi et al.[19] reported that a remarkable improvement in leg pain was observed at 3 months after condoliase injection in patients in their teens and 20s. However, they did not compare the clinical outcomes of the participants with those of patients aged >20 years. Therefore, this study aimed to determine whether the efficacy and safety of condoliase therapy for LDH in patients aged <20 years are comparable to those in patients aged ≥20 years.

Materials and Methods

Patient recruitment

This retrospective study was conducted in accordance with the principles of the Declaration of Helsinki and approved by our institutional review board (No. 23-240). The requirement for informed consent was waived due to the retrospective nature of the study. Patients who received intradiscal condoliase injections for LDH between August 2018 and August 2022 at our department and who underwent follow-up assessments for at least 1 year were evaluated. Intradiscal condoliase injection was recommended for the following conditions: confirmed unilateral lower-extremity pain with evidence of nerve root compression from a herniated disk on magnetic resonance imaging (MRI), presence of neurological signs corresponding to the affected nerve root distribution, and a lack of response to conservative treatments. For patients aged <20 years, skeletal maturity was confirmed by evaluating the Risser grade and assessing the lumbar endplate. Condoliase therapy was indicated in patients with Risser grade ≥4 and epiphyseal stage of the vertebral body[20]. To confirm the absence of limbus vertebrae, preoperative computed tomography (CT) was performed. Administration of condoliase therapy was determined based on adequate informed consent. Patients aged >70 years were excluded from the study.

A total of 189 patients with LDH who received condoliase injections during the study period were identified. Among them, 3 who had spondylolisthesis, 13 who had advanced age (>70 years), and 35 who were lost to follow-up were excluded. The remaining 138 patients (93 men, 46 women; mean age, 41.3±15.4 years; mean follow-up period, 40.1±14.6 months) were included in the final analysis.

Procedure

The patient assumed a semilateral decubitus position, and the imaging arm was properly positioned to ensure parallel visualization of the adjacent endplates of the disk. Guided by fluoroscopy, a 21-gage needle for disk puncture was inserted into the intervertebral disk on the side opposite to the herniation. Condoliase was dissolved in 1.2-mL saline to prepare a 1.25-U/mL solution. After properly positioning the needle tip at the center of the disk, a single 1-mL dose was administered. All injections were performed under local anesthesia by certified spinal surgeons with extensive training in the intradiscal injection technique. After the injection, the patient was closely monitored for 2 h to ensure immediate safety. In general, it is advised to wait for a minimum of 3 months after a condoliase injection to evaluate its efficacy before contemplating surgery. However, in instances of excessively severe pain, the attending physician may opt for surgery in less than 3 months based on their evaluation.

Data collection and clinical assessment

Patient data, including age, sex, herniation level, history of discectomy at the same level as the intradiscal injection, duration of symptoms before injection, and adverse events, were obtained from the medical records of each patient. The visual analog scale (VAS) scores for leg and back pain and the Oswestry Disability Index (ODI) were assessed at baseline and at the 3-month and 1-year follow-ups. Condoliase therapy was considered to be effective for patients showing an improvement in VAS scores of 50% or greater for leg pain compared with baseline during the 1-year follow-up and who did not need surgery. Conversely, it was considered ineffective for patients with an improvement in VAS scores of less than 50% or those requiring surgical intervention.

Radiographic assessment

The MRI results were analyzed at baseline, 3 months, and 1 year after the injection. The disk height was determined at the midpoint of the endplate using the central slice of the sagittal image. The extent of disk degeneration was evaluated using the Pfirrmann grading system[21]. The images were compared to evaluate changes in disk height, disk degeneration, and herniation size. The disk height recovery rate was calculated as follows: (1-year disk height−3-month disk height)/(baseline disk height−3-month disk height)×100. A disk height recovery rate of more than 50% was defined as disk height recovery[10]. Furthermore, a decline in Pfirrmann grade between baseline and 3 months was defined as Pfirrmann grade deterioration. Patients showing an improvement in Pfirrmann grade from 3 months to 1 year were classified as demonstrating Pfirrmann grade recovery. Three spi-

Table 1. Comparison of Demographic Characteristics between Groups Y (Young) and A (Adult).

	Group Y (n=15)	Group A (n=123)	*P*-value
Age (y)	17.5±1.5	44.2±13.7	<0.001*
Female	7 (46.7%)	39 (31.7%)	0.924
Herniation level			0.767
L1/2	0	2 (1.6%)	
L2/3	0	2 (1.6%)	
L3/4	0	6 (4.9%)	
L4/5	6 (42.1%)	56 (45.5%)	
L5/S	9 (47.4%)	57 (46.3%)	
Symptom duration (months)	8.4 [2–26]	7.4 [1–60]	0.124
History of discectomy at the same level	0	6 (4.9%)	0.495
Posterior intervertebral angle ≥5°	2 (13.3%)	8 (6.5%)	0.297
Pfirrmann classification			<0.001*
Grade II	5 (33.3%)	7 (5.7%)	
Grade III	10 (66.7%)	95 (77.2%)	
Grade IV	0	21 (17.1%)	
Herniation type			0.456
Subligamentous	14 (93.3%)	108 (87.8%)	
Transligamentous	1 (6.7%)	15 (12.2%)	
Disc height (mm)	8.3±1.7	8.0±1.8	0.511
VAS for leg pain (cm)	7.2±2.4	6.8±2.6	0.544
VAS for back pain (cm)	4.4±3.8	5.9±2.6	0.114
ODI	35.6±21.7	43.5±19.0	0.112

Continuous data are expressed as mean±standard deviation (range). Categorical data are expressed as number (%). Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index. *P<0.05

nal surgeons performed a radiographic assessment and decided Phirmann grade and the change in herniation size on the basis of majority consensus.

The patients were divided into two groups according to age: young (<20 years: Group Y) and adult (20-70 years: Group A). Demographic data, radiographic parameters, and clinical outcomes were compared between the groups. In Group Y, a comparative analysis was conducted between patients who effectively responded to condoliase therapy and those for whom the treatment was ineffective.

Statistical analysis

The Shapiro-Wilk test was used to assess the normal distribution assumptions of the data. Student's *t*-test and the Mann-Whitney U test were utilized to examine differences between the groups for continuous variables and the chi-squared test and Fisher's exact test for categorical data. Repeated-measures analysis of variance, followed by the Bonferroni test, was employed to evaluate the statistical significance of differences across each period. Statistical analyses were conducted using SPSS (version 23.0; SPSS Inc., Chicago, IL, USA), with the significance level set at P<0.05.

Results

None of the patients developed anaphylactic shock or neurological sequelae after the intradiscal condoliase injection. However, four patients developed rashes within 3 days of the injection, but it resolved with standard dermatological treatment. Furthermore, there were no cases of disk herniation recurrence after the injection.

A total of 15 patients aged <20 years (Group Y) and 123 patients aged 20-70 years (Group A) were identified. Compared with Group A, Group Y exhibited a substantially lower Pfirrmann classification grade, whereas no intergroup differences were observed in sex, herniation level, symptom duration, history of discectomy at the same level, posterior intervertebral angle ≥5°, herniation type, preoperative disk height, VAS scores for leg and back pain, and ODI (Table 1).

Surgical treatment was subsequently required in 13 patients (3 patients [20.0%] in Group Y and 10 patients [8.1%] in Group A). Group Y had a higher proportion of patients who required surgery; however, the difference was not statistically significant. In Group Y, six patients exhibited insufficient improvement (three patients who required surgery and three patients who showed an improvement of <50% in the VAS score for leg pain); thus, condoliase therapy was effective in nine patients (60.0%). Contrarily, among the 123 patients in Group A, 27 showed insufficient improvement (10 patients who required surgery and 17 patients who showed an improvement of <50% in the VAS score for leg pain); thus, condoliase therapy was effective in 96 patients (78.0%). Group Y tended to show a lower incidence of efficacy; however, this difference was not statistically signifi-

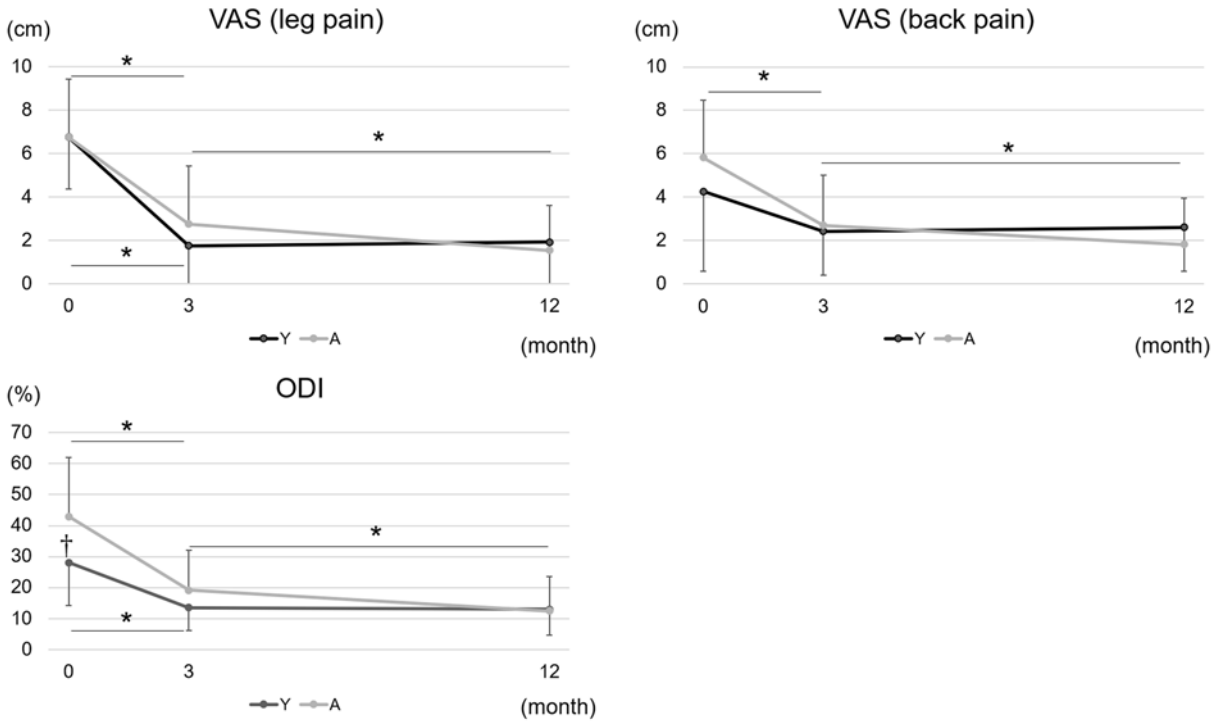

Figure 1.

Changes over time in the Oswestry Disability Index and visual analog scale scores after condoliase injection in the young (Group Y) and adult (Group A) groups. Error bars represent the standard deviation. *Statistically significant change relative to baseline. †Statistically significant differences between the two groups at each point.

Table 2. Comparison of MRI Changes between Groups Y (Young) and A (Adult).

	Group Y (n=12)	Group A (n=107)	*P*-value
Pfirrmann grade deterioration	10 (83.3%)	49 (45.8%)	0.014*
Pfirrmann grade recovery	5/10 (50.0%)	8/49 (16.3%)	0.033*
Disc height recovery rate (DHRR) (%)	63.6±34.2	33.8±36.8	0.009*
Disc height recovery (DHRR >50%)	8 (72.7%)	26 (34.6%)	0.016*
Reduction of herniation	10 (83.3%)	88 (82.2%)	0.925

Continuous data are expressed as mean±standard deviation (range). Categorical data are expressed as number (%). Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index. *P<0.05

cant.

Among the patients who did not require surgery after condoliase therapy, the mean VAS scores (leg and back pain) and ODI at 3 months after injection substantially improved compared with the baseline in both groups Y and A (P<0.05), and no intergroup differences were observed, except in the preoperative ODI (Fig. 1). Although Group A showed a substantial improvement at 1 year in comparison with the corresponding values at 3 months, no differences were observed in Group Y (Fig. 1).

All MRI data were obtained for 119 patients, including 12 and 107 in Groups Y and A, respectively. The rates of Pfirrmann grade deterioration and recovery were considerably higher in Group Y than in Group A (83.3% vs. 45.8% [P<0.05, Table 2] and 50.0% vs. 16.3% [P<0.05; Table 2], respectively). Furthermore, the disk height recovery rate (disk height recovery rate >50%) and the mean disk height recovery rate were considerably higher in Group Y than in Group A (72.7% vs. 34.6% [P<0.05; Table 2] and 63.6% vs. 33.8% [P<0.05], respectively). However, the rate of reduction in herniation did not substantially differ (Table 2). Although the disk height in Group Y tended to decrease more at 3 months, it recovered to the same level as that in Group A at 1 year (Fig. 2).

The demographic data and clinical outcomes of the patients in Group Y are summarized in Table 3. Condoliase therapy was effective in 9 of the 15 patients (Fig. 3) and ineffective in the remaining 6 patients (Fig. 4). None of the patients showed increased lumbar spine instability or worsening of lower back pain within 1 year of injection. When patients who positively responded to the treatment were compared with patients who did not, the latter showed a considerably higher preoperative ODI (P<0.05; Table 4). The efficacy of condoliase therapy was insufficient in the

two patients who showed posterior intervertebral angle ≥5° (Table 4).

Discussion

We investigated the efficacy of condoliase therapy in patients with LDH aged <20 years and compared the results with those obtained in adult patients. Patients aged 20-70 years were established as the control group in this study as previous clinical trials included patients within this age range[7,8]. In the appropriate use criteria, condoliase administration to young individuals (aged <20 years) is not contraindicated but should be performed with caution because of the possibility of developing lumbar vertebral instability resulting from intradiscal administration. Although condoliase therapy in young patients has demonstrated short-term safety without spinal instability, long-term follow-up data are essential to assess its potential side effects.

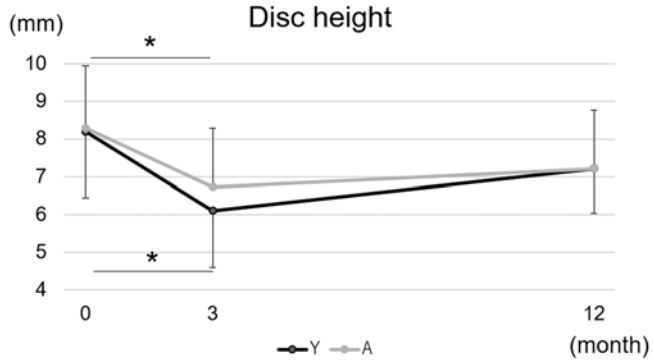

Figure 2.
Time course of changes in disk height in the young (Group Y) and adult (Group A) groups. Error bars represent standard deviation. *Statistically significant changes in comparison with baseline.

In Group Y in the present study, 3 of the 15 patients (20.0%) required surgery after condoliase therapy due to insufficient pain relief. This rate tended to be higher than that in Group A (8.1%), although the difference was not statistically significant because of the limited number of cases. Furthermore, Group Y tended to show a lower efficacy rate than Group A (60.0% vs. 78.0%). The efficacy rate in Group Y in the present study was also slightly lower than that previously reported[9-18]. While the exact reason for these findings is uncertain, in young patients, greater lumbar spine mobility, increased activity levels, and the presence of a herniated disk with epiphyseal cartilage may have potentially influenced the unfavorable outcomes[22]. Nevertheless, surgery could be successfully avoided in 80% of the cases, indicating that condoliase therapy may be a viable treatment option for LDH. Compared with surgery, chemonucleolysis has the advantages of minimal invasiveness, fewer postoperative adhesions, quicker remobilization, and lower costs. Therefore, it can be considered to be an alternative to surgery in patients resistant to conservative treatment.

The main concern associated with this treatment is the potential risk of progressive disk degeneration after intradiscal condoliase injection, as the dissolution of the nucleus pulposus has been shown to promote disk degeneration after chemonucleolysis. The reported incidence of Pfirrmann grade progression after condoliase injection ranges from 41.3% to 57.1%[7,9-11,13,16]. In this study, Group Y exhibited a substantially lower preoperative Pfirrmann grade, indicating less intervertebral disk degeneration, than Group A (Table 1). Although none of the cases showed new-onset instability,

Table 3. Details of Patients below 20 Years Old.

Age	Sex	Level	Symptom duration (month)	Posterior opening (>5°)	Pfirrmann grade			Leg pain VAS (cm)		Back pain VAS (cm)		ODI		Reduction of herniation	Adverse events	Outcome
					pre	3m	1y	pre	1y	pre	1y	pre	1y			
15	F	L4/5	3	No	3			10		10		73		No	No	Surgery
17	M	L5/S	5	No	2	3		7		0		40		No	No	Surgery
17	F	L5/S	3	Yes	3	4		10		5		84		No	No	Surgery
18	F	L4/5	12	No	3	3	3	6	5	8	2	24	16	Yes	No	Ineffective
19	M	L4/5	2	Yes	2	3	3	8	5	8	6	48	22	Yes	No	Ineffective
15	F	L5/S	8	No	3	3	3	7	4	0	5	36	20	No	No	Ineffective
19	M	L4/5	11	No	2	3	3	4	0	0	0	10	0	No	No	Effective
17	F	L5/S	2	No	3	4	3	2	1	2	1	7	2	Yes	No	Effective
15	F	L5/S	12	No	3	4	3	5	2	0	0	27	12	Yes	No	Effective
19	M	L5/S	8	No	3	4	3	9	0	6	3	38	14	Yes	No	Effective
19	M	L5/S	10	No	3	4	4	8	3	10	3	40	20	Yes	No	Effective
17	F	L4/5	12	No	3	4	3	10	2	6	4	44	24	Yes	No	Effective
18	M	L5/S	5	No	2	3	3	9	1	6	2	33	14	Yes	No	Effective
18	M	L5/S	7	No	2	3	3	8	0	0	0	12	0	Yes	No	Effective
19	M	L4/5	26	No	3	4	3	5	0	5	4	18	12	Yes	No	Effective

Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index

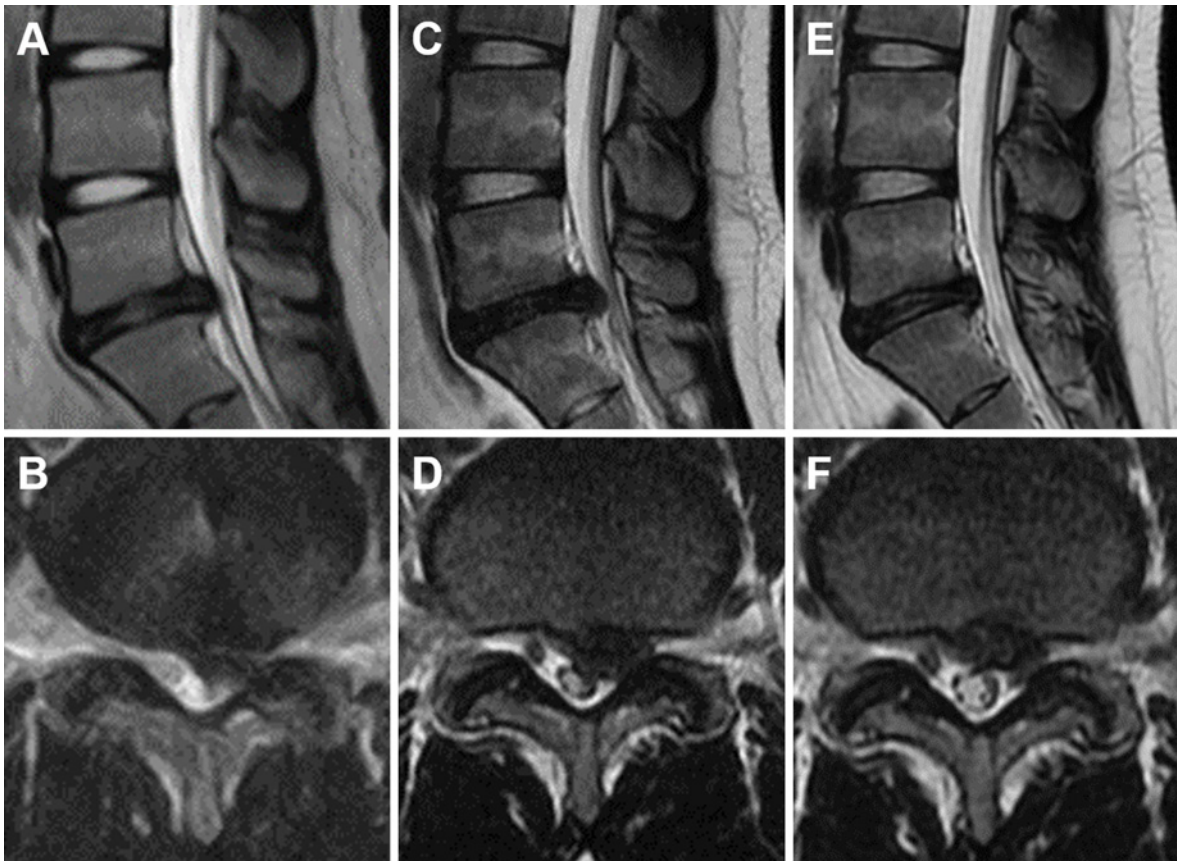

Figure 3. Case 1: A 19-year-old man complaining of left lower-extremity pain for 8 months.
Baseline sagittal (A) and axial (B) T2-weighted magnetic resonance imaging (MRI) scans showing disk herniation at L5/S. Sagittal and axial MRI scans obtained 3 months (C and D) and 1 year (E and F) after condoliase injection. The disk height and signal changes at 3 months after injection were lower than those observed before the injection. The patient had recovered at 1 year and showed a reduction in disk herniation.

a considerably higher rate of Pfirrmann grade deterioration was observed in Group Y (83.3%), whereas it was 45.8% at 3 months in Group A (Table 2). Conversely, Group Y exhibited a considerably higher rate of Pfirrmann grade recovery (50.0% vs. 16.3%), a considerably higher disk height recovery rate (63.6% vs. 33.8%), and the same disk height level as that of Group A at 1 year (Table 2, Fig. 2). Kobayashi et al.[23] also reported that younger age (<40 years) and Pfirrmann Grade II or III at baseline were associated with progression of the Pfirrmann grade after condoliase therapy. These results indicate that young patients with less disk degeneration are at risk of progression to disk degeneration when they receive condoliase injection. Contrarily, Banno et al. reported that some patients demonstrated disk height recovery in previously degenerated disks after condoliase therapy. They demonstrated that this phenomenon was more frequently observed in young patients, indicating that disk degeneration induced by chemonucleolysis can be resolved, particularly in young patients. Kobayashi et al.[19] showed that progression of Pfirrmann criteria on MRI at 3 months after injection occurred in 61.5% of the cases. However, disk degeneration induced by chemonucleolysis recovered, particularly in patients with an early change in the Pfirrmann criteria. Sugimura et al.[24] conducted an experimental study using monkeys and reported that the glycosaminoglycan content relatively recovered 28 weeks after condoliase injection. The effect of chemonucleolysis on the nucleus pulposus was temporary. Furthermore, after the enzyme activity disappeared, the intervertebral disk could regenerate. Regarding the timing of this recovery, Banno et al.[10] reported that recovery of disk height and signal intensity was observed at 12 months, comparing with 3 months. Moreover, Kobayashi et al.[19] demonstrated that recovery has already been observed at 6 months after condoliase injection. These results indicate that there might be a potential for a shift toward regeneration between 3 and 6 months particularly in young patients.

Although none of the patients showed adverse events, including symptoms such as worsening of lower back pain due to intervertebral disk degeneration, the long-term effects of condoliase on the intervertebral disk remain unknown; thus, careful observation is warranted.

It was found that in young patients, condoliase therapy tended to be less effective in those with a posterior intervertebral angle ≥5° and a worse preoperative ODI score, although the number of cases was limited (Table 4). The surgical treatment outcomes of adolescent patients with LDH were reported to be more favorable than those of adult pa-

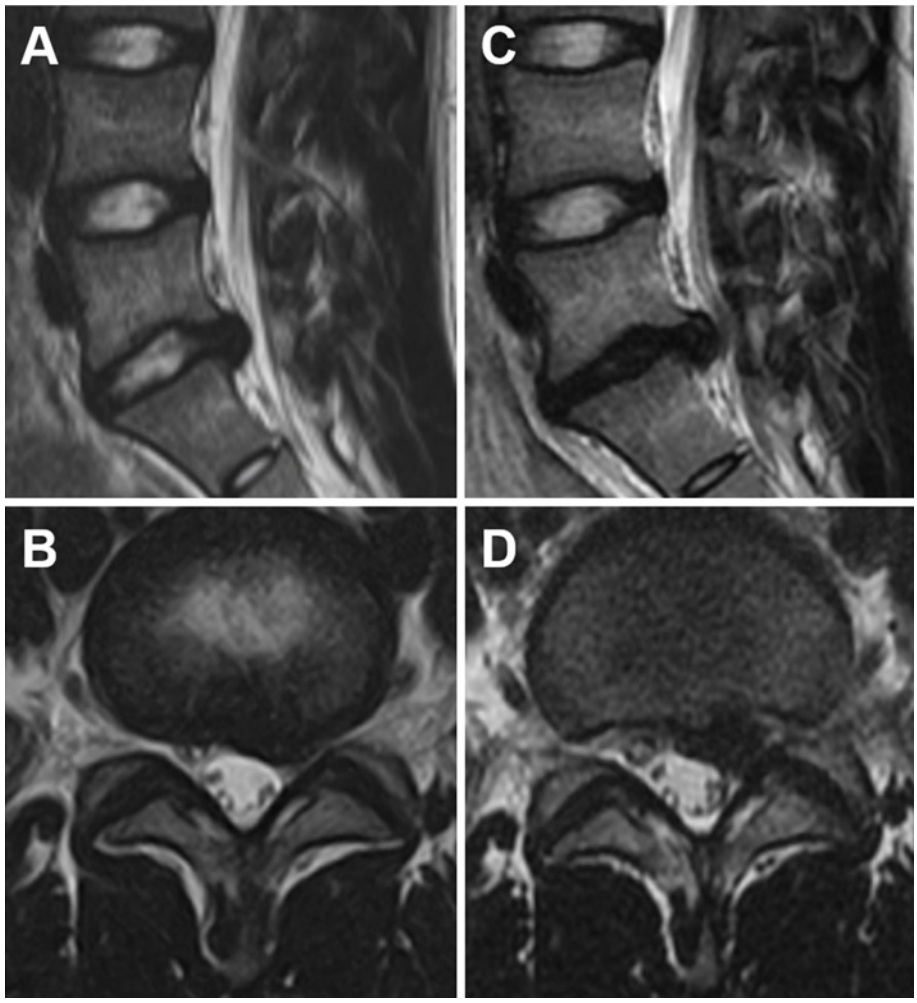

Figure 4. Case 1: A 17-year-old man complaining of left lower-extremity pain for 8 months.
Baseline sagittal (A) and axial (B) T2-weighted magnetic resonance imaging (MRI) scans showing disk herniation at L5/S. Sagittal and axial MRI scans obtained 3 months (C and D) after condoliase injection showed no reduction in disk herniation. The patient underwent surgery 6 months after the injection due to persistent pain.

tients[22,25-27]. However, Strömqvist et al.[27] reported that severe preoperative pain, poor mental health, and severe disability are risk factors for worse clinical outcomes. When considering condoliase administration in young patients, caution should be taken when managing patients showing segmental instability or in those experiencing severe pain and disability. Furthermore, considering the frequent occurrence of the limbus vertebrae in young patients, CT scans should be performed before treatment to rule out cases involving the limbus vertebrae.

This study has some limitations that need to be acknowledged. First, the number of enrolled young patients was relatively small, and the follow-up period was short. Further clinical studies involving a larger number of patients with longer follow-up periods are warranted to confirm the efficacy of condoliase therapy in young patients. Moreover, evaluations over an extended period are crucial to determine whether the intervertebral disk degeneration caused by condoliase therapy leads to back pain or lumbar instability. Second, disk height was not evaluated using standing X-rays. Accurate assessment of intervertebral disk height is better achieved using standing X-rays than MRI.

Conclusions

Chemonucleolysis with condoliase may have limited efficacy in patients aged <20 years. Thus, caution should be taken when managing patients with lumbar instability or a preexisting disability. Although chemonucleolysis with condoliase is a less invasive treatment option for LDH, its administration should be decided upon sufficient consent considering the potential limited efficacy and possible disk degeneration.

Conflicts of Interest: Y.Y., G.Y., H.A., K.I., T.Y., K.K., and Y.M. have nothing to disclose.

T.B. belongs to the division as follows; Donated Fund Laboratory (Department of Surgical care, Morimachi, Hama-

Table 4. Comparison of Demographic Characteristics between Patients with Effective and Ineffective for Condoliase Therapy in Group Y.

	Effective (n=9)	Ineffective (n=6)	*P*-value
Age (y)	17.9±1.4	16.8±1.6	0.224
Female	3 (33.3%)	4 (66.7%)	0.924
Herniation level			0.455
L4/5	3 (33.3%)	3 (50.0%)	
L5/S	6 (66.7%)	3 (50.0%)	
Symptom duration (months)	10.3 [2–26]	5.5 [2–12]	0.145
Posterior intervertebral angle ≥5°	0	2 (33.3%)	0.143
Pfirrmann classification			0.713
Grade II	3 (33.3%)	2 (33.3%)	
Grade III	6 (66.7%)	4 (66.7%)	
Herniation type			0.600
Subligamentous	8 (88.9%)	6 (100.0%)	
Transligamentous	1 (11.1%)	0	
Disc height (mm)	7.8±1.7	9.1±1.5	0.181
VAS for leg pain (cm)	6.7±2.7	8.0±1.7	0.388
VAS for back pain (cm)	3.9±3.6	5.2±4.3	0.607
ODI	25.4±14.1	50.8±23.1	0.036*

Continuous data are expressed as mean±standard deviation (range). Categorical data are expressed as number (%). Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index. *P<0.05

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Ethical Approval: This study design was approved by the appropriate ethics review boards in Hamamatsu University School of Medicine (IRB No. 23-240).

Informed Consent: Patient informed consent was waived considering the retrospective nature of the research.

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