Disc degeneration could be recovered after chemonucleolysis with condoliase. −1 year clinical outcome of condoliase therapy−

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-1 year clinical outcome of condoliase therapy-

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IRB approval

All study participants provided informed consent, and the study design was approved by the appropriate ethics review boards in Hamamatsu University School of Medicine (No. 18-220) and all patients provided written informed consent.

Conflict of interest

We have nothing to disclose.

Abstract

Background

Condoliase-induced chemonucleolysis is a less-invasive alternative treatment for lumbar disc herniation (LDH); however, its long-term clinical outcome is still unclear. This study aimed to investigate 1-year clinical outcomes and assess radiographs after chemonucleolysis with condoliase.

Methods

We enrolled patients with LDH who received condoliase injection with a follow-up period of >1 year. Sixty patients (37 men, 23 women; mean age, 44.5 ± 18.9 years; mean follow-up period, 22.0 ± 6.0 months) were analyzed. Changes in disc height and degeneration were evaluated using magnetic resonance imaging. Visual analog scale (VAS) scores for leg and back pain and the Oswestry disability index (ODI) were obtained. All data were assessed at baseline, 1-month, 3-month, and 1-year follow-up.

Results

Surgical treatment was subsequently required in 8 patients (12.5%) after condoliase therapy. Their ODI and VAS scores for leg pain and back pain significantly improved at 1 year, as in those who received condoliase therapy only. On MRI, progression of Pfirrmann grade was observed in 23 patients (44.2%) at 3 months; however, 8 patients recovered to baseline at 1 year. The mean disc height decreased at 3 months; however, it recovered at 1 year. Disc height recovery (disc recovery rate >50%) was observed in 30.8% of the patients. Patients with disc height recovery were significantly younger than those without. Patients with longer symptom duration (≥1 year) showed significantly lower rates of effectiveness compared with those with

shorter symptom durations (<1 year).

Conclusions

Chemonucleolysis with condoliase is a safe and minimally invasive treatment. Disc degeneration induced by chemonucleolysis could be recovered, particularly in younger patients. Prolonged symptom duration had adverse effects on outcome; thus, therapeutic intervention at the optimal time is needed.

Introduction

Chemonucleolysis is a less invasive treatment for lumbar disc herniation (LDH), which induces chemical dissolution of the nucleus pulposus of the intervertebral disc [1-3]. It is considered an intermediate procedure between conservative and surgical treatment. Chemonucleolysis with chymopapain for the treatment of LDH was first reported by Smith in 1964 [4]. It has been widely used as an alternative treatment for LDH in the 1980s and 1990s throughout Europe and the United States, with excellent clinical outcomes [5-7]. Chemonucleolysis with chymopapain is safer, with an overall mortality rate of 0.019%, than surgery [8]. However, chymopapain is currently unavailable for use because of its severe adverse events, including anaphylaxis, infection, hemorrhage, and neurological events [7]. Chondroitin sulfate ABC endolyase (condoliase) is a pure mucopolysaccharidase derived from the gram-negative rod *Proteus vulgaris* [9]. Condoliase has high substrate specificity for chondroitin sulfate and hyaluronic acid, which are glycosaminoglycans of proteoglycans and abundant in the nucleus pulposus [10]. In contrast to chymopapain, condoliase lacks protease activity, thus inducing chemonucleolysis with less damage to the surrounding tissues, such as nerves and vessels [11-13]. In clinical phase III studies, condoliase shows significantly better improvements in leg pain compared with placebo without any significant adverse events [14, 15]. Based on these results, this treatment has been approved in Japan for clinical use for LDH [16]. It has been widely used in patients with LDH since it became clinically available in 2018. The reported effectiveness of this treatment is 70%–85% without any major adverse event [17, 18]. After condoliase injection, decreased

herniation size is frequently observed; however, disc degeneration progresses as well by dissolution of the nucleus pulposus. In a previous work, Banno et al. [17] revealed that 35.7% of the patients showed decreased disc height of ≥ 20%, 42.9% showed progression of disc signal change, and 61.9% showed a reduction in disc herniation after condoliase injection within 3 months. On the other hand, Szypryt et al. [6] reported a slight recovery of disc height and signal change after chemonucleolysis by chymopapain at 1 year compared with 1 month after injection. However, the long-term effects of condoliase on intervertebral disc degeneration and clinical outcomes remain unclear. Therefore, the objective of this study was to investigate 1-year clinical outcomes and assess radiographs after chemonucleolysis with condoliase in patients with LDH.

Materials and Methods

Patient recruitment

This study was approved by the institutional review board of our institution (No. 18-220), and all patients provided written informed consent. We retrospectively evaluated the patients who received intradiscal condoliase injection for LDH since August 2018 in our department and completed a minimum follow-up of 1 year. The following conditions were indications for intradiscal condoliase injection: unilateral lower extremity pain with or without back pain, nerve root compression by a herniated disc confirmed using magnetic resonance imaging (MRI), neurological signs consistent with the distribution of the compressed nerve root, and resistance to conservative treatment. In contrast, the contra-indications were as follows:

cauda equine syndrome, severe and progressive motor deficit, multi-segmental nerve root symptoms due to multilevel disc herniation, and other spinal disorders. We excluded patients with trans-ligamentous herniation and spondylolisthesis from the analysis. We identified 97 patients with LDH who were administered condoliase injection between August 2018 and March 2020 at our institute. Among them, 17 patients who were lost to follow-up, 6 with spondylolisthesis, 10 with trans-ligamentous herniation, and 4 with inadequate data were excluded. In total, 60 patients (37 men, 23 women; mean age, 44.5 ± 18.9 years; mean follow-up period, 22.0 ± 6.0 months) were finally enrolled in this study.

Procedure

The patient was placed in a semi-lateral decubitus position, and the image arm was adjusted so that adjacent endplates of the disc were visualized in parallel. Under fluoroscopic guidance, a 21-gauge disc-puncture needle was inserted from the contralateral side of the herniation into the intervertebral disc. Condoliase was dissolved in 1.2 mL of saline to prepare a 1.25 U/mL solution. After confirming that the needle tip was positioned in the center of the disc, a single 1 mL dose was injected. All injections were performed under local anesthesia by registered board-certified spinal surgeons who were well trained in the intradiscal injection technique. All patients were carefully monitored for 2 h after injection to ensure immediate safety and were allowed to return home without prophylactic antibiotic administration.

Data collection and clinical assessment

The following demographic and clinical data were extracted from medical charts: age, sex, herniation level, history of discectomy at the same level as intradiscal injection, duration of symptoms before injection, and adverse events. To assess pain intensity and health-related quality of life, we collected data on the visual analog scale (VAS) for leg and back pain and the Oswestry disability index (ODI) at baseline, 1-month, 3-month, and 1-year visit. Patients whose VAS for leg pain improved by 50% or more at 1 year from baseline and did not require surgery were defined as effective for condoliase therapy.

We generally do not perform operations for 3 months after condoliase injection to judge the effect; however, if the pain is extremely severe to tolerate, the operation is decided by each doctor even within that period.

Radiographic assessment

The MRI results were examined at baseline and 3 months and 1 year after injection. Disc height was calculated at the midpoint of the end plate based on the central slice of the sagittal image. The degree of affected-disc degeneration was assessed using the Pfirrmann classification system [19]. Images were compared to evaluate changes in disc height, disc degeneration, and herniation size. Disc height recovery rate was calculated as follows: (1 year disc height – 3 month disc height) / (baseline disc height – 3 month disc height) × 100. Disc height recovery rate of more than 50% was defined as disc height recovery. In addition, Pfirrmann grade recovery between 3 months and 1 year was defined as disc degeneration recovery. Radiographic assessment was performed by three spine surgeons and decided by the majority consensus. The intra- and inter-observer reliabilities of disc height measurement was assessed using the intra-class correlation coefficient (ICC).

Statistical analysis

We divided the patients into those who needed surgery at the same level after injection due to ineffectiveness of condoliase therapy during the follow-up periods (group O) and those who did not require surgery after injection (group C). Additionally, in group C, the patients were divided according to whether or not the disc height recovered. Furthermore, we compared the outcome according to preoperative symptom duration: symptom duration less than 1 year (short duration, group S) and 1 year and more (long duration, group L). Demographic data and radiographic parameters were compared between these groups using the Student's t-test, Mann–Whitney U test, chi-squared test, and Fisher exact test. All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL, USA). A p-value of <0.05 was considered statistically significant.

Results

Patient demographic data and baseline characteristics are summarized in Table 1. None of the patients developed anaphylactic shock or any neurologic sequelae. Four patients experienced rash within 3 days of injection, which was resolved with standard dermatological treatment. No patients demonstrated new-onset spondylolisthesis after condoliase therapy. Of the 64 patients who were followed up for >1 year, surgical treatment was subsequently required in 8 (12.5%) (group O). Among the 60 patients whose entire data were

obtained, 13 showed insufficient improvement (8 patients with operation and 5 patients with VAS improvement of <50% for leg pain); therefore, condoliase therapy was effective in 47 patients (78.3%). The mean operative period was 3.4 months (0–10 months) after condoliase injection. Four patients experienced temporary pain relief; however, they needed surgery because of the recurrence of pain. Three patients reported no pain relief, and one patient showed deteriorated symptoms after condoliase injection due to an increase in herniation size that required an emergency operation. No intergroup differences in age, sex, herniation level, symptom duration, history of discectomy, and disc degeneration were observed between groups O and C (Table 2). VAS scores (leg pain and back pain) and ODI significantly improved from baseline to 1-year post-treatment in both groups, and no intergroup differences were observed at each time point (Figure 1). In 52 patients who did not require surgical treatment after condoliase treatment (group C), the mean VAS scores (leg pain and back pain) and ODI were significantly improved from 1 month to 1 year after injection compared with baseline ($p < 0.01$) (Figure 2).

With regard to MRI findings, 39 patients (75.0%) showed a reduction in disc herniation size at 1 year. Comparison of MRI findings before and 3 months after injection showed progression of Pfirrmann grade in 23 patients (44.2%); however, only 8 patients (15.4%) recovered to baseline at 1 year. The mean disc height significantly decreased at 3 months after injection (8.4–6.8 mm, $p < 0.05$); however, it significantly recovered at 1 year (6.8–7.3 mm, $p < 0.05$) (Figure 3). The intra- and inter-observer ICC of disc height were 0.983 and 0.942, respectively. The disc height recovery rate was 31.4% on average, and 16 patients (30.8%) showed positive outcomes in this process (disc height recovery rate >50%). Patients with disc height recovery were

significantly younger; however, no significant differences were found in sex, herniation level, symptom duration, history of discectomy, and disc degeneration between the groups (Table 3). Moreover, patients with disc height recovery had a higher incidence of Pfirrmann grade recovery than those without disc height recovery (38% vs. 6%) (Table 3).

The patients were divided according to the duration of symptoms; 42 patients (70.0%) had short symptom duration (< 1 year) (group S) and 18 (30.0%) had long symptom duration (≥ 1 year) (group L). The number of patients who required surgery was four (9.5%) in group S and four (22.2%) in group L. The number of patients who showed effectiveness (VAS of leg pain improvement ≥50% from baseline) of condoliase therapy was 36 (85.7%) in group S and 11 (61.1%) in group L. The rate of effectiveness was significantly lower in group L; however, no differences were found in age, sex, herniation level, symptom duration, history of discectomy, disc degeneration, VAS score, and ODI between the groups (Table 4).

Case presentation

The patient, an 18-year-old female with L5/S-disc herniation, exhibited right lower extremity pain consistent with the distribution of compressed nerve roots. Pain relief was achieved 2 weeks after condoliase injection without any adverse event. Decreases in disc height and signal change were observed at 3 months after injection compared with pre-injection. They recovered at 1 year, accompanied by reduction of the herniated disc (Figure 4).

Discussion

We showed that sufficient pain relief was achieved in 78.3% of patients with LDH over 1 year by chemonucleolysis with condoliase. Consistent with other reports [14, 18], significant improvement in pain was observed at 3 months after injection, and the condition of patients was maintained until 1 year (Figure 2). In clinical phase III studies, condoliase showed significant improvement in leg pain compared with placebo, and the improvement was maintained until 52 weeks after injection [14]. However, we showed that 12.5% of the patients who underwent condoliase therapy for LDH subsequently required surgery within 1 year. Age, sex, herniation level, symptom duration, or disc degeneration showed no significant association (Table 1). Previous reports revealed that this treatment could be less effective for patients with older age, a history of discectomy, a history of epidural or nerve root block, spondylolisthesis, and spinal instability [17, 18]. Similarly, the ODI and VAS scores for leg pain and back pain in patients who required surgery after condoliase therapy significantly improved at 1 year compared with those who underwent only condoliase therapy. Therefore, identifying the optimal time for surgery in cases with insufficient effect after chemonucleolysis with condoliase is crucial.

Progressing disc degeneration by dissolution of the nucleus pulposus is one of the adverse events of chemonucleolysis with condoliase, with a reported incidence of 41.3% to 53.7% based on the Pfirrmann grade progression [14, 17, 18]. In this study, although no new onset of instability occurred, progression of Pfirrmann grade was observed in 23 patients (44.2%) at 3 months. Among them, 8 patients (15.4%)

recovered to baseline at 1 year. Moreover, disc height recovery (disc recovery rate > 50%) was observed in 30.8% of the patients. Szypryt et al. [6] reported some cases with slight disc height reconstitution and signal intensity recovery at 1 year compared with 1 month after chemonucleolysis with chymopapain. Chemonucleolysis by condoliase was less invasive for around tissue than that by chymopapain [20]; however, the long-term effects of condoliase on the intervertebral disc remain unknown. An experimental study reported regeneration of intervertebral discs after chemonucleolysis [11, 20, 21]. For clinical application, we showed that disc height loss was 20% on average at 3 months and recovered to 13% at 1 year after condoliase injection. Sugimura et al. [20] conducted an experimental study using monkeys and reported that glycosaminoglycan content somewhat recovered 28 weeks after injection of condoliase. The effect of chemonucleolysis on the nucleus pulposus was temporary, and after the enzyme activity disappeared, the intervertebral disc could be regenerated. Interestingly, this phenomenon was observed in younger patients (Table 3). By contrast, discectomy promotes disc height loss of 18% at 3 months and progresses to 26% at 2 years after surgery [22]. Intradiscal condoliase injection indeed promotes disc degeneration, and the impact is likely to be less than that of discectomy.

The long prognosis of LDH was good, and sufficient pain relief was achieved even when treated conservatively [23]. A cohort study revealed that the pain in approximately half of the patients lasted for over 1 year, and prolonged leg pain duration was identified as one of the negative prognostic factors [24, 25]. The present study found that the rate of patients who responded to treatment was lower in patients with a symptom duration of > 1 year (Table 4). Many reports have revealed that prolonged duration of symptoms

has negative effects on postoperative outcome in patients with LDH [25-28]. Therefore, ineffective conservative treatment should not be continued endlessly, and intervention at the optimal time is important. The present study had two main limitations. First, the number of cases enrolled was relatively small. Second, the mean follow-up period of 22.0 ± 6.0 months was short. Further clinical surveys involving a larger number of patients with longer follow-up periods are needed to determine the prognostic factors for condoliase therapy and changes in disc degeneration. Third, we did not compare the clinical outcomes between patients who underwent intradiscal condoliase therapy and conservative controls. Spontaneous reduction in disc herniation is frequently observed, especially in the case of trans-ligamentous herniation; thus, a good prognosis can be expected using conservative treatment [29, 30]. Chiba et al. [14] revealed that decreases in herniated mass volumes were observed significantly more frequently in the condoliase group than in the control group.

However, to the best of our knowledge, our study revealed favorable clinical outcomes for patients with LDH treated using chemonucleolysis with condoliase over a 1-year follow-up.

Conclusions

Chemonucleolysis with condoliase is safe, highly effective, and minimally invasive. It could be an alternative treatment for LDH; however, 12.5% of the patients required surgical treatment within 1 year after condoliase therapy. Disc degeneration induced by chemonucleolysis could be recovered, particularly in younger patients.

Prolonged duration of symptoms had adverse effects on outcome; thus, therapeutic intervention at the optimal time is crucial.

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Figure legends

Figure 1

Comparison of the Oswestry disability index and visual analog scale following condoliase injection between groups O and C.

Abbreviations: C, condoliase group; O, operation after condoliase group. * indicates $p<0.05$

Figure 2

Bar graphs of changes in the Oswestry disability index (ODI) and visual analog scale (VAS) following condoliase injection. The ODI and VAS for back and leg pain improved significantly at 1 month, 3 months, and 1 year after injection ($p < 0.05$). * indicates $p<0.05$

Figure 3

Time course change of disc height. The mean disc height was significantly decreased at 3 months after injection; however, it significantly recovered at 1 year ($p < 0.05$).

Figure 4

Case 1: An 18-year-old woman.

Baseline sagittal (A) and axial (B) T2-weighted magnetic resonance images (MRI) showing disc herniation at L5/S. Sagittal and axial MRI taken 3 months (C and E) and 1 year (D and F) after condoliase injection.

Figure 1

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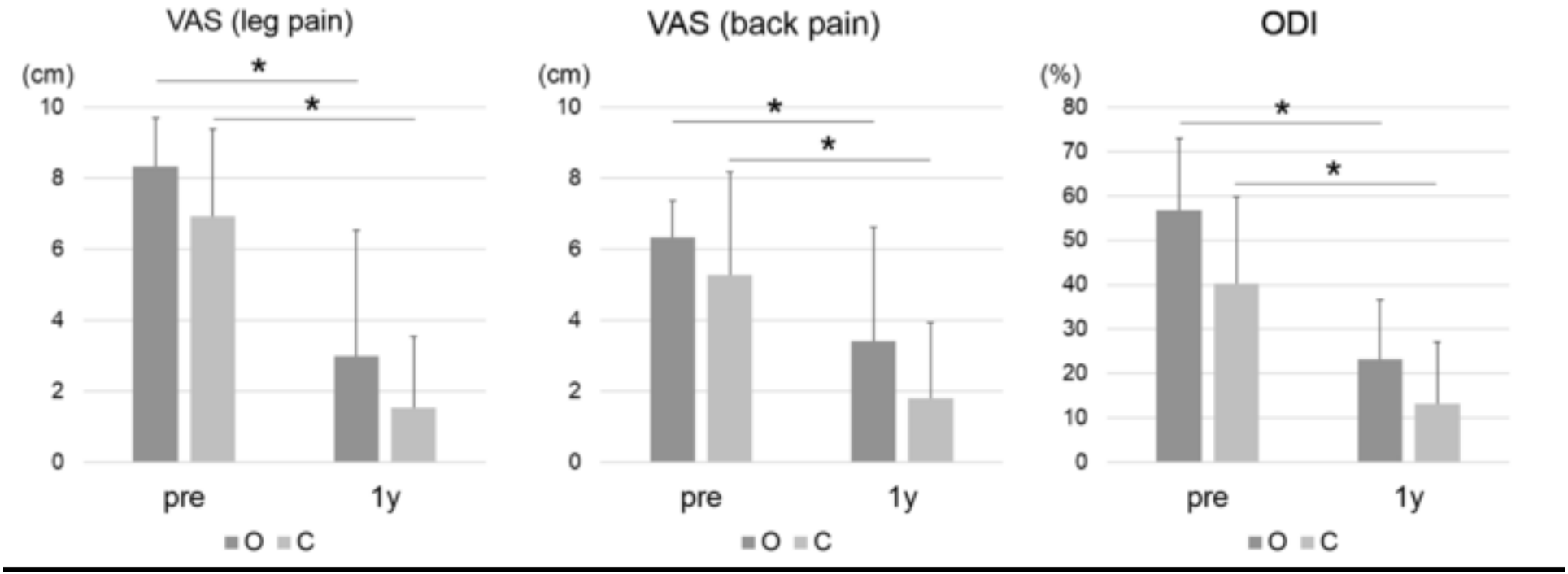

Figure 2

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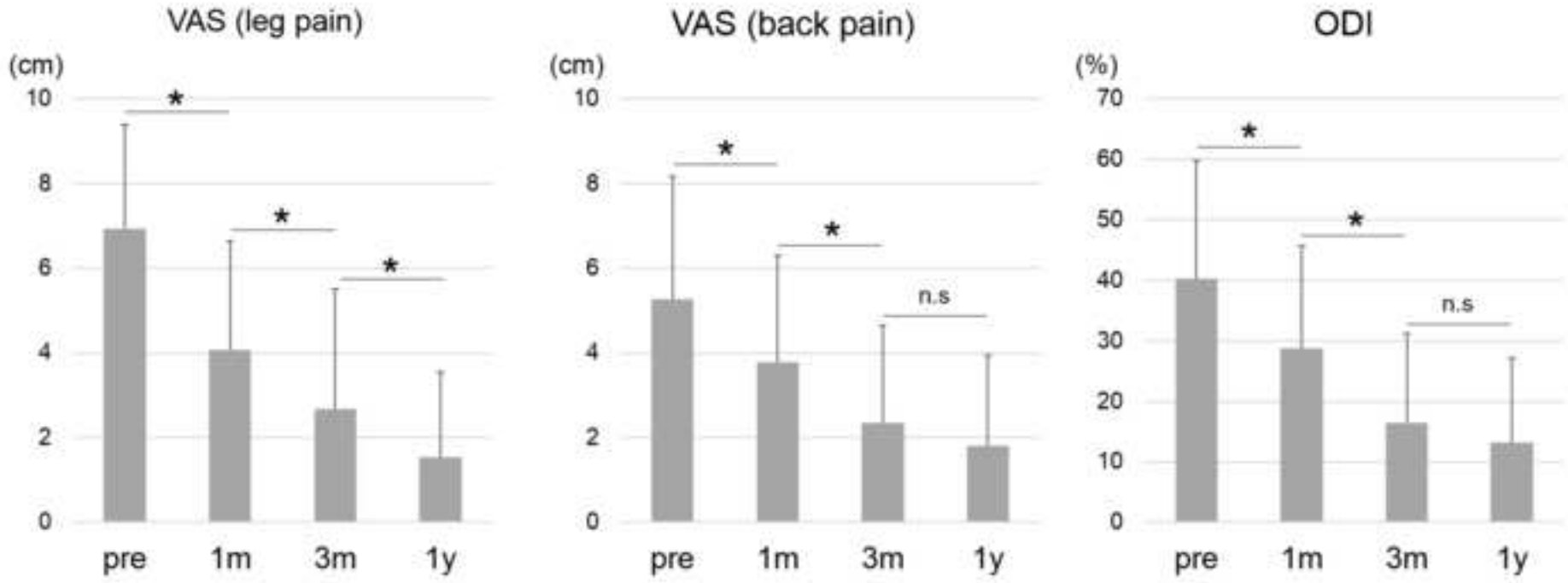

Figure 3

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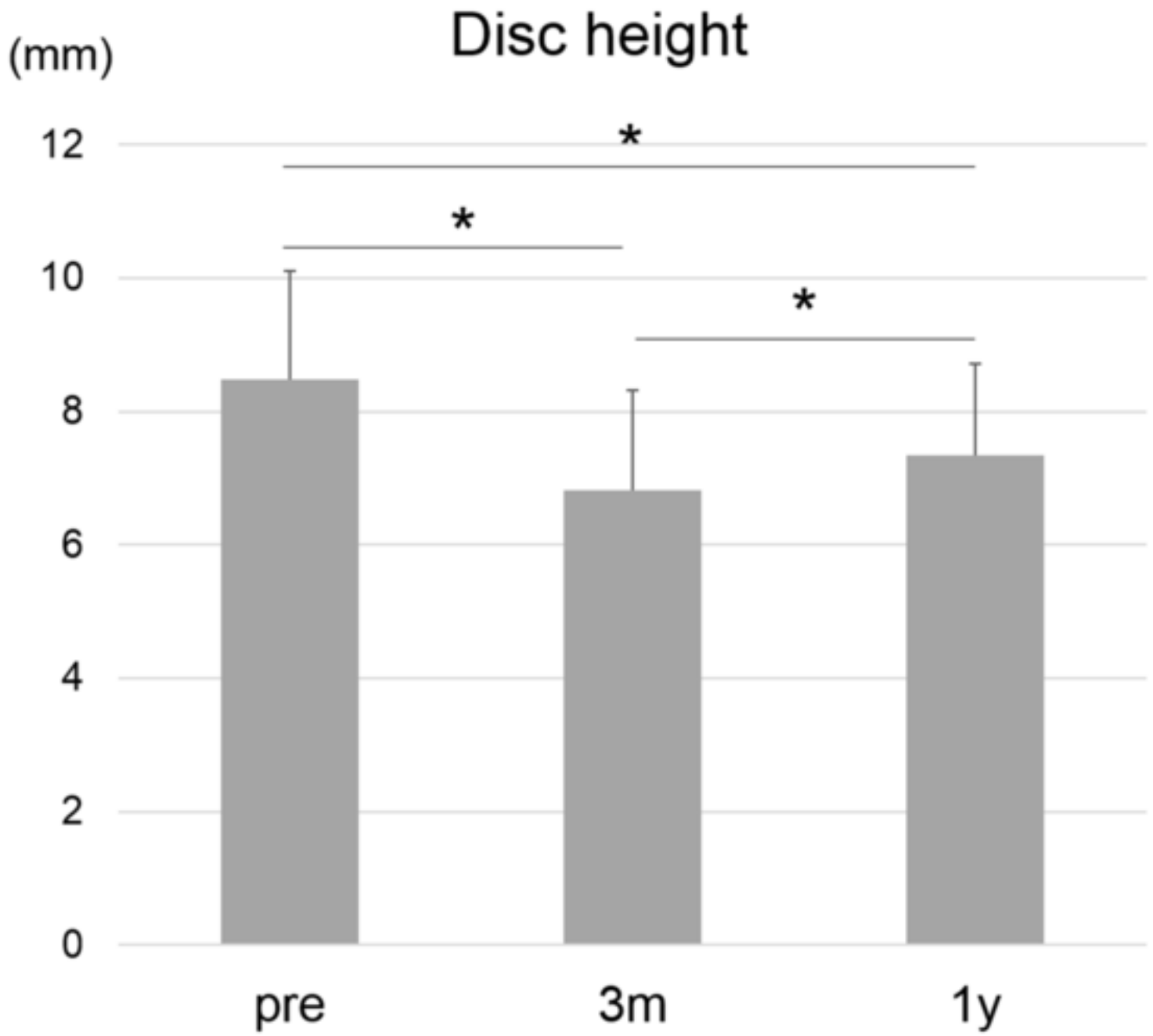

Figure 4

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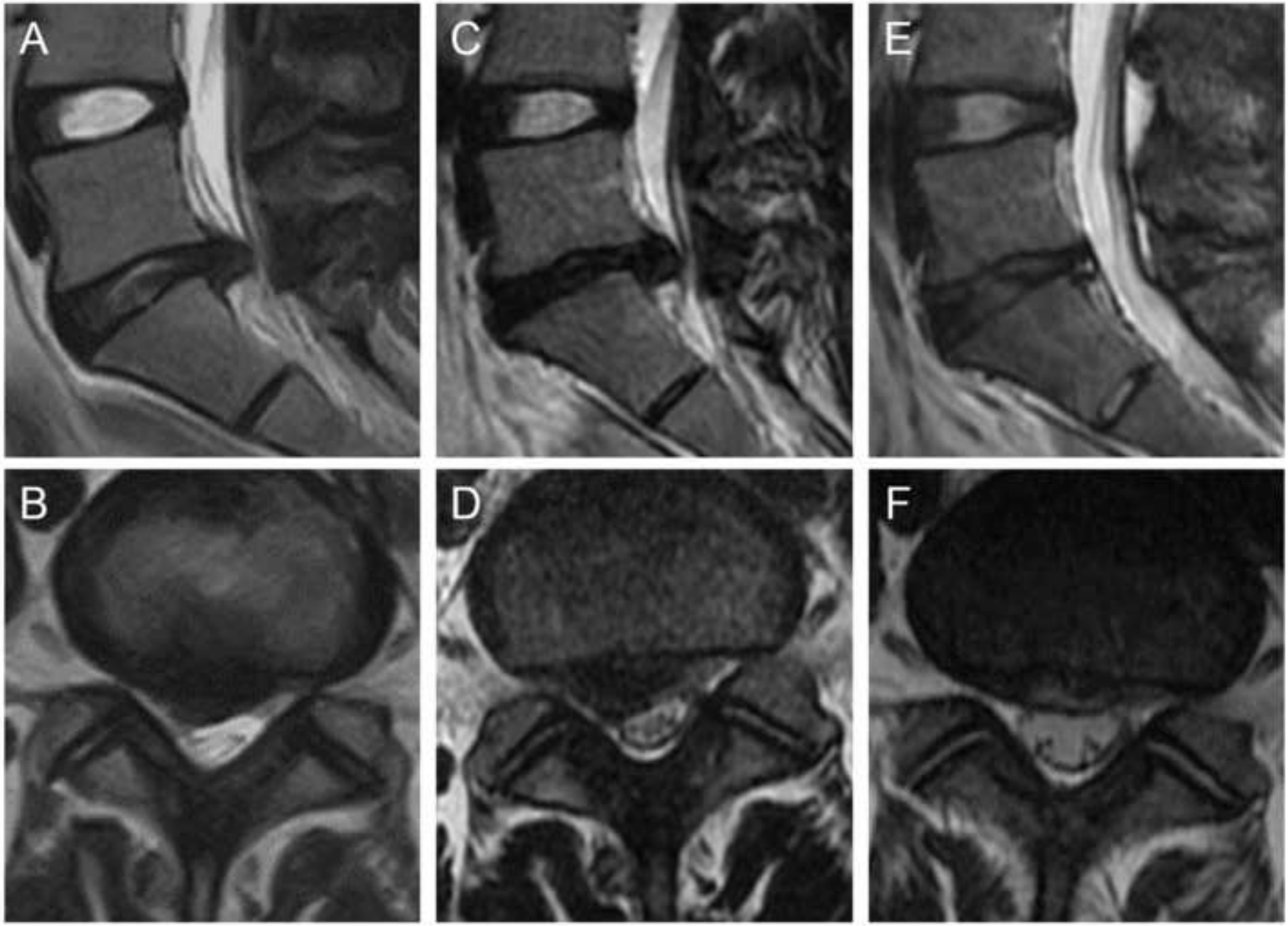

Table 1 Demographic and baseline characteristics of the patients

Variables	Data (n=60)
Age (years)	44.5 ± 18.9
Female	23 (38.3%)
Herniation level	
L2/3	1 (1.7%)
L3/4	4 (6.7%)
L4/5	26 (43.3%)
L5/S	29 (48.3%)
Symptom duration (months)	10 [1–60]
History of discectomy at the same level	6 (10.0%)
Pfirrmann classification	
Grade II	4 (6.7%)
Grade III	47 (78.3%)
Grade IV	9 (15.0%)
Disc height (mm)	8.4 ± 1.6
VAS for leg pain (cm)	7.3 ± 2.2
VAS for back pain (cm)	5.4 ± 2.8
ODI (%)	42.2 ± 19.7

Continuous data are presented as mean ± standard deviation of median [range]. Categorical data are presented as number (%). Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index.

Table 2 Comparison of demographic and baseline characteristics of groups C and O

	Group C (n = 52)	Group O (n = 8)	p-value
Age (y)	44.4 ± 19.6	45.6 ± 15.2	0.695
Female	19 (36.5%)	4 (50.0%)	0.361
Herniation level			0.833
L2/3	1 (1.9%)	0	
L3/4	4 (7.7%)	0	
L4/5	22 (42.3%)	4 (50.0%)	
L5/S	25 (48.1%)	4 (50.0%)	
Symptom duration (months)	9.4 ± 10.4	15.0 ± 13.3	0.419
History of discectomy at the same level	4 (7.7%)	2 (25.0%)	0.178
Pfirrmann classification			0.770
Grade II	3 (5.8%)	1 (12.5%)	
Grade III	41 (78.8%)	6 (75.0%)	
Grade IV	8 (15.4%)	1 (12.5%)	
Disc height (mm)	8.5 ± 1.6	8.2 ± 1.6	0.664

Continuous data are presented as mean ± standard deviation of median [range]. Categorical data are presented as number (%). Abbreviations: C, condoliase group; O, operation after condoliase group.
*$p<0.05$

Table 3 Comparison of imaging findings between the patients with and without disc height recovery.

		Disc height recovery (+) (n = 16)	Disc height recovery (-) (n = 36)	p-value
Age (y)		25.1 ± 7.5	52.9 ± 17.0	<0.001*
Female		6 (37.5%)	13 (36.1%)	0.924
Herniation level				0.176
L2/3		0	1 (2.8%)	
L3/4		0	4 (11.1%)	
L4/5		5 (31.3%)	17 (47.2%)	
L5/S		11 (68.8%)	14 (38.9%)	
Symptom duration (months)		9.5 ± 9.1	9.4 ± 11.1	0.965
History of discectomy at the same level		2 (12.5%)	2 (5.6%)	0.360
Pfirrmann classification				0.205
Grade II		0	2 (5.6%)	
Grade III		15 (93.8%)	26 (72.2%)	
Grade IV		1 (6.3%)	8 (22.2%)	
Pfirrmann grade recovery		6 (37.5%)	2 (5.6%)	0.007*
Preoperative disc height (mm)		8.2 ± 1.2	8.6 ± 1.8	0.358
VAS for leg pain (cm)	baseline	6.2 ± 2.3	7.2 ± 2.5	0.224
	3 month	2.4 ± 2.6	2.8 ± 3.0	0.711
	1 year	1.2 ± 1.6	1.7 ± 2.2	0.414
VAS for back pain (cm)	baseline	4.8 ± 2.5	5.5 ± 3.1	0.461
	3 month	2.5 ± 2.3	2.3 ± 2.3	0.790
	1 year	2.0 ± 1.7	1.7 ± 2.3	0.694
ODI (%)	baseline	33.1 ± 19.2	43.5 ± 19.1	0.099
	3 month	15.8 ± 14.4	16.8 ± 15.2	0.836
	1 year	12.0 ± 9.7	13.8 ± 15.5	0.700

Continuous data are presented as mean ± standard deviation of median [range]. Categorical data are presented as number (%). Abbreviations: VAS, visual analog scale; ODI, Oswestry Disability Index.
*p<0.05

Table 4 Comparison of demographic and baseline characteristics of groups S and L

	Group S (n = 42)	Group L (n = 18)	p-value
Age (y)	44.1 ± 18.2	45.6 ± 21.1	0.787
Female	15 (35.7%)	8 (44.4%)	0.524
Herniation level			0.150
L2/3	1 (2.4%)	0	
L3/4	2 (4.8%)	2 (11.1%)	
L4/5	15 (35.7%)	11 (61.1%)	
L5/S	24 (57.1%)	5 (27.8%)	
Symptom duration (months)	5.0 ± 3.1	22.6 ± 13.0	<0.001*
History of discectomy at the same level	3 (7.1%)	1 (5.6%)	0.653
Pfirrmann classification			0.587
Grade II	3 (7.1%)	1 (5.6%)	
Grade III	34 (81.0%)	13 (72.2%)	
Grade IV	5 (11.9%)	4 (22.2%)	
Disc height (mm)	8.5 ± 1.6	8.3 ± 1.8	0.586
VAS for leg pain (cm)	7.2 ± 2.3	7.4 ± 2.0	0.830
VAS for back pain (cm)	5.1 ± 2.7	6.1 ± 2.9	0.265
ODI (%)	44.6 ± 19.5	36.5 ± 19.8	0.182
Required operation	4 (9.5%)	4 (22.2%)	0.347
Effectiveness (VAS of leg pain improvement ≥50%)	36 (85.7%)	11 (61.1%)	0.041*

Continuous data are presented as mean ± standard deviation of median [range]. Categorical data are presented as number (%). Abbreviations: S, short symptom duration; L, long symptom duration; VAS, visual analog scale; ODI, Oswestry Disability Index.

*$p<0.05$