Clinical outcome of condoliase injection treatment for lumbar disc herniation: Indications for condoliase therapy

Title: Clinical outcome of condoliase injection treatment for lumbar disc herniation:

Indications for condoliase therapy

A**uthors**: Tomohiro Banno, M.D., Ph.D., Tomohiko Hasegawa, M.D., Ph.D., Yu Yamato, M.D., Ph.D., Go Yoshida M.D., Ph.D., Tatsuya Yasuda., M.D., Hideyuki Arima, M.D., Ph.D., Shin Oe, M.D., Hiroki Ushirozako, M.D., Tomohiro Yamada, M.D., Koichiro Ide, M.D., Yu Watanabe, M.D., Yukihiro Matsuyama, M.D., Ph.D.

Affiliation: Department of Orthopaedic Surgery, Hamamatsu University School of Medicine, Hamamatsu, Shizuoka, Japan

Corresponding Author's name and complete mailing address:

Tomohiro Banno, M.D, PhD.

Department of Orthopaedic Surgery

Hamamatsu University School of Medicine

1-20-1 Handayama, Higashi-ku, Hamamatsu, Shizuoka 431-3192, Japan

Phone: +81-53-435-2299; Fax: +81-53-435-2296; Email: tomohiro.banno0311@gmail.com

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 is a novel, potent chemonucleolytic drug available for clinical use for lumbar disc herniation (LDH) in Japan. The aim of this study was to assess the clinical outcome of condoliase therapy in patients with LDH, as well as factors affecting the clinical outcome.

Methods

We enrolled patients with LDH who were receiving condoliase injection. The following baseline data were collected: symptom duration; herniation level and type; T2 signal intensity of herniation; adverse events; rates of spondylolisthesis, posterior intervertebral angle of ≥5°, and vertebral body translation of ≥3 mm. Change in disc height, disc degeneration, herniation size, visual analogue scale (VAS) for leg and back pain, and Oswestry Disability Index (ODI) were evaluated at the baseline, and 3-month follow-up. These data were compared between patients with efficacious (VAS improvement of ≥20 mm; group E) and inefficacious (VAS improvement <20 mm or required operation; group I) for condoliase treatment.

Results

Forty-seven patients (20 women, 27 men; mean age 48 years) were included. The herniation level was L2/3 in one patient, L3/4 in two, L4/5 in 23, and L5/S1 in 21. Median symptom duration was 8 months. The mean VAS and ODI improved significantly from the baseline to 3-month follow-up (p

< 0.01). Group E included 33 patients (70.2%) and group I included 14, three of whom had a history of discectomy. The rates of spondylolisthesis and posterior intervertebral angle ≥5° were significantly higher in group I than in group E. However, the rates of trans-ligamentous type and herniation with high signal intensity on T2-weighted images (highT2) were significantly higher in group E. Reduction of disc herniation was more frequently observed in group E.

Conclusions

Condoliase injection resulted in significantly improved symptoms in patients with LDH. Condoliase therapy was less effective for patients with a history of discectomy, spondylolisthesis, or those with a posterior intervertebral angle ≥5°, while trans-ligamentous type and high T2 herniation were associated with increased efficacy.

Introduction

Lumbar disc herniation (LDH) occurs when degenerated nucleus pulposus and annulus fibrous bulge from intervertebral disc and compress nerve root. The condition typically manifests as symptoms such as leg pain, low back pain, and numbness. In most cases, successful pain relief can be achieved through conservative treatment [1, 2]. However, prolonged periods of treatment, which restrict daily activities, can cause substantial social problems, and can become a financial burden due to loss of productivity [3]. Some reports have described surgical treatment as having higher cost-effectiveness than conservative treatment once the effects on productivity are considered [4]. Surgical intervention should therefore be considered when symptoms have not improved after an adequate period of conservative treatment.

Although surgical treatment offers several advantages, it carries the risk of surgical complications [5, 6]. Chemonucleolysis is a less invasive treatment for LDH which induces chemical dissolution of the nucleus pulposus of the intervertebral disc [7-9]. This treatment is considered an intermediate treatment between conservative and surgical treatment. The utility of chemonucleolysis with chymopapain has been widely reported in patients throughout Europe and the United States, with excellent clinical outcomes [10-12]. Adverse events include anaphylaxis, infection, hemorrhage, and neurological events; although, with an overall mortality rate of 0.019%, the risks are significantly

lower than those associated with surgical complications [13].

Chondroitin sulfate ABC endolyase (condoliase) is a pure mucopolysaccharidase derived from the gram-negative rod, *Proteus vulgaris* [14]. Condoliase has high substrate specificity for chondroitin sulfate and hyaluronic acid, which are glycosaminoglycans (GAGs) of proteoglycans and are abundant in the nucleus pulposus [15]. Unlike chymopapain, condoliase lacks protease activity, thus inducing chemonucleolysis without disturbing the nerve and ligamentous tissues [16].

Through clinical phase III studies, suitable therapeutic dosage [17] as well as the efficacy and safety of chemonucleolysis with condoliase have been determined in patients with LDH [18]. Condoliase has been approved by the drug regulatory authority in Japan as an intradiscal treatment for LDH [19]. However, clinical phase III studies only included patients with a sub-ligamentous type of LDH at the L4/L5 or L5/S1 levels, and excluded patients with trans-ligamentous LDH, foraminal LDH, or those with no history of lumbar surgery [17, 18]. The effect of condoliase on the case of trans-ligamentous, foraminal, and recurrence LDH is still unknown. Therefore, the present study aimed to investigate the clinical outcome of chemonucleolysis with condoliase for patients with LDH, and to assess the factors related to clinical outcome.

Materials and Methods

Patient recruitment

This prospective study was approved by the Institutional Review Board of our institution (No. 18-220) and all patients provided written informed consent. We recruited patients with all types of LDH after obtaining written informed consent in order to evaluate the effectiveness of condoliase. We enrolled patients who had received intradiscal condoliase injection for LDH since August 2018, in our department, and had completed a minimum of 3 months of follow up. The following conditions were indications for intradiscal condoliase injection: 1) unilateral lower-extremity pain with or without back pain, 2) nerve-root compression by herniated disc confirmed by magnetic resonance imaging (MRI), 3) neurological signs consistent with distribution of the compressed nerve root, and 4) resistance to conservative treatment such as medication and anesthetic block for at least 1 month. The exclusion criteria were: 1) cauda equine syndrome, 2) severe and progressive motor deficit, and 3) multi-segmental nerve-root symptoms due to multilevel disc herniation. Condoliase injection is allowed at only a single level, and once in a patient's lifetime in order to prevent the production of antibodies against condoliase, which may cause anaphylaxis.

Procedure

The patient was placed in a semi-lateral decubitus position, and a 21-gauge disc-puncture needle was inserted from the contralateral side of herniation, under fluoroscopic guidance. 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 observed for 2 hours after injection to monitor the appearance of anaphylactic reactions. After confirming the vital stability, they were allowed to return home without the administration of prophylactic antibiotics.

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, and adverse events. To assess pain intensity and health-related quality of life, we collected data using a visual analogue scale (VAS) for leg and back pain, as well as evaluating the Oswestry Disability Index (ODI), at the baseline and at 3-month follow-up.

Radiographic assessment

Lumbar radiographs were examined before injection. The posterior intervertebral angle was defined on a lateral-flexion radiograph as the angle between the vertebral endplates adjacent to the intervertebral disc to be injected. Vertebral translation was defined as the absolute difference in the distance between the posterior edges of the upper and lower vertebral bodies adjacent to the

intervertebral disc to be injected on a lateral flexion-extension radiograph [17]. The rates of spondylolisthesis (defined as ≥3 mm vertebral slipping based on the lateral-lumbar radiograph), posterior intervertebral angle of ≥5°, and vertebral body translation of ≥3 mm were investigated.

The MRI results were examined prior to and 3 months after injection. The type of herniation (sub-ligamentous extrusion, trans-ligamentous extrusion, or foraminal), signal intensity of herniation (occurrence of high intensity on T2-weighted images [highT2]) were evaluated (Figure 1). 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. Images taken prior to and 3 months after injection were compared to evaluate changes in disc height, disc degeneration, and herniation size. Radiographic assessment was performed by three spine surgeons and decided by majority consensus. The reduction in herniation was also decided by majority consensus of three spine surgeons.

Statistical analysis

Patients were categorized into two groups according to the change in VAS for leg pain. If the values prior to and 3 months after injection revealed an improvement indicated by a change of 20 mm or more on the scale, the treatment was considered to have been effective. These patients were categorized into group E (efficacious). Patients who required lumbar operation or reported a VAS

improvement of less than 20 mm were categorized into group I (inefficacious). Demographic data and radiographic parameters were compared between the two groups. Comparing the data between the baseline and 3-month follow-up, we excluded five patients who required operation within 3 months after injection. Continuous variables were first assessed for normality using the Shapiro-Wilk test and analyzed using the paired t-tests or Wilcoxon signed-rank test, as appropriate, and categorical variables were tested using the Chi-square test or Fisher's exact test, as appropriate. 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

Of 63 patients with LDH who received condoliase injection between August 2018 and May 2019 at our institute, 16 were excluded because of the following reasons: 10 patients were lost to follow-up, two had rheumatoid arthritis, two had other spinal disease, one had no MRI, and one did not complete the questionnaire. A total of 47 patients, 20 women and 27 men, were finally enrolled in this study. The mean age at the time of condoliase injection was 48.0 ± 17.7 (15-81) years, and the patients were followed-up for a mean period of 34 weeks (12–48 weeks). Patient demographic data and baseline characteristics are summarized in Table 1. The median value of symptom duration before injection

was 8 months (range: 1-60). Three patients had history of discectomy at the same level. Muscle weakness (grade 4 in manual muscle testing) was observed in six patients (12.8%). Baseline VAS for leg pain and back pain were 71 mm and 51 mm, respectively, and ODI was 44.6%. The herniation types were sub-ligamentous extrusion in 33 patients (70.2%), trans-ligamentous extrusion in 13 patients (27.7%), and foraminal herniation in one patient (2.1%), respectively.

With respect to efficacy, the mean VAS (leg pain and back pain) and ODI were significantly improved at 3 months compared with baseline levels ($p < 0.01$), excluding five patients who required operation within 3 months (Figure 2). At 3 months after injection, pain relief (indicated by VAS change ≥20 mm) was achieved in 33 patients (70.2%), while eight patients reported insufficient pain relief (VAS change <20 mm), with six requiring operation. No patient developed anaphylactic shock or appearance of any neurological deterioration within 3 month after injection. One patient experienced a rash within 1 day of injection; this resolved with standard dermatological treatment. One patient with L5/S herniation developed foraminal stenosis at the level of injection, which caused L5-nerve-root symptoms and required operation.

Comparing group E and group I, condoliase did not work well on patients who had received discectomy at the same level. There were no significant differences in age, sex, herniation level, or symptom duration between the groups (Table 2). With regard to imaging findings, the rate of spondylolisthesis and posterior intervertebral angle of ≥5° were significantly higher in group I. In

addition, the rate of trans-ligamentous type and herniation with highT2 were significantly higher in group E ($p<0.05$) (Table 3).

Comparing MRI findings of the baseline and 3 months after injection (excluding five patients who could not undergo 3-month MRI examination due to operation), decreased disc height of ≥20% was observed in 15 patients (35.7%), progression of Pfirrmann grade was observed in 18 patients (42.9%), and 26 patients (61.9%) showed a reduction in disc herniation. Reduction in disc herniation was more frequently observed in group E ($p<0.01$) (Table 4).

Case presentation

Case 1

The patient, a 50-year-old woman with L5/S-disc herniation, exhibited right-lower-extremity pain consistent with the distribution of compressed nerve roots. Conservative treatment for more than 10 months was ineffective. Pain relief was achieved 2 weeks after condoliase injection without any adverse events. The VAS for leg pain improved significantly from 100 mm at the baseline to 20 mm at 3 months after treatment. Sub-ligamentous herniation was reduced 3 months after injection, as revealed by MRI (Figure 3).

Case 2

The patient, a 68-year-old man with L4/5-disc herniation, exhibited right-lower-extremity pain consistent with the distribution of compressed nerve roots. Conservative treatment for more than 4 months was ineffective. Pain relief was achieved 2 weeks after condoliase injection without any adverse events. The VAS for leg pain improved significantly from 40 mm at the baseline to 0 mm at 3 months after treatment. Trans-ligamentous herniation was found, from T2-weight signal intensity, to be reduced 3 months after injection (Figure 4).

Discussion

To the best of our knowledge, this is the first report to assess the clinical outcome and related factors of condoliase therapy for patients with LDH, including trans-ligamentous and foraminal type LDH. The ODI and VAS of patients with LDH improved significantly by 3 months after intradiscal injection of condoliase. Despite previous failures of conservative treatment, 70.2% of the enrolled patients experienced improvements in pain levels following condoliase injection. In cases where resistance to conservative treatment is observed, excellent clinical outcome has traditionally been achieved through surgical treatment. The need to reduce operative risks, invasiveness, and therefore achieve early rehabilitation, has driven the development of less invasive techniques [20]. However, many of these procedures are associated with a high initial cost and slow learning curve. Chemonucleolysis is easier,

cheaper, and less invasive than operation, and avoids many of the problems of other minimally invasive techniques. Although serious adverse events such as anaphylaxis, vascular, or neurological complications were not reported in the present study, one patient experienced a rash after injection of condoliase. Allergic reaction after condoliase injection has been reported to have an incidence of 5% [18]. Similar to chymopapain [8, 9, 21], allergic reaction is a relatively frequent adverse event which should be considered. In the present study, one case of foraminal stenosis occurred at the same level as the injection. This complication has never been reported previously; it may be that chemonucleolysis induced a decrease in disc height which lead to progression of foraminal stenosis.

In terms of influencing factors for condoliase therapy, history of herniotomy, spondylolisthesis, or posterior intervertebral angle of ≥5° were associated with reduced effectiveness of condoliase therapy, while trans-ligamentous type herniation with a highT2 was associated with increased effectiveness.

In cases where previous discectomy has been performed, the presence of fibrosis may inhibit chemonucleolysis and result in an unfavorable outcome. Furthermore, spondylolisthesis and spinal instability may have negative effects on condoliase therapy.

Spontaneous reduction in disc herniation is frequently observed in the case of trans-ligamentous herniation; thus, a good prognosis can be expected for this type of herniation [22, 23]. Migration of herniation to the epidural space via the posterior longitudinal ligament exposes the vascular supply causing an inflammatory response and macrophage phagocytosis, thus leading to herniation resorption

[22]. In trans-ligamentous herniation, condoliase may reach the trans-ligamentously extruded nucleus pulposus and promote an immunologic reaction, resulting in the reduction of disc herniation and pain relief. We noted a case in which herniation protruded to the foramen, which was successfully treated by condoliase injection. To remove foraminal-type herniation, facet breakage and segmental fusion are usually required. Condoliase therapy offers considerable advantages in this context, as fusion surgery may be avoided.

A high intensity zone (HIZ) on the T2-weighted image was frequently observed in herniated disc at the baseline. This has been reported to correlate with discogenic low back pain [24, 25]. Peng et al. [24] revealed that, based on histological analysis, ingrowth of vascularized granulation tissue induces an immunoreaction and recruitment of inflammatory cells in the HIZ. Rasekhi et al. [26] reported that herniation with high signal intensity on the T2-weighted image reflects hydrated disc herniation and is associated with a significantly shorter duration of pain. We report that hemonucleolysis by condoliase induces dehydration of the nucleus pulposus, and is thus a more effective treatment for highT2 herniation.

Komori et al. [22] investigated the medical history of patients with lumbar-disc herniation from MRI findings, and found clinical outcome to be correlated with a reduction in disc herniation. In the present study, while 9 out of 16 patients experienced pain relief with no reduction in herniation, most patients (73%) reported pain relief accompanied with reduction in herniation (Table 4).

Because chemonucleolysis promotes disc degeneration by dissolution of the nucleus pulposus, disc height decreased and disc degeneration progressed to some degree after injection, consistent with a previous study [17]. The long-term disc height changes after chemonucleolysis, by chymopapain, have been reported to be almost the same as that observed after discectomy [27]. Szypryt et al. [11] assessed MRI changes after chemonucleolysis and reported a slight reconstitution of disc height at 1 year compared with 1 month after injection. Additionally, in 4 out of 13 cases, the signal intensity of intervertebral disc showed a slight recovery at 1 year from 1 month after injection. The long-term effects of condoliase on the intervertebral disc and surrounding tissues are still unclear, and should be further examined.

Although there is evidence that surgical discectomy produces better clinical outcomes than chemonucleolysis [28], this treatment is considered an intermediate between conservative and surgical treatment for LDH. However, compared with surgical treatment, the lower rate of complications [12] and relatively lower cost suggest that chemonucleolysis by condoliase may become an alternative to surgical treatment. In the present series, except for one case with a long duration of symptoms (>1 year), significant pain relief was achieved by condoliase injection. Therefore, this approach is a treatment option which could be considered before operation.

This study has several limitations which should be acknowledged. First, the 3-month follow-up period was short; thus, we should continue with further evaluation in order to clarify the long-term efficacy

and complications of condoliase therapy. Second, as the sample size was small and no major adverse event was observed, this study was not sufficient to evaluate the safety of condoliase. Unlike chymopapain, condoliase degrades GAGs specifically and lacks protease activity [15]. Therefore, condoliase is less likely to cause damage to the intervertebral disc and surrounding tissues. However, in order to fully assess the safety of condoliase, further clinical surveys involving a larger number of patients are required.

Conclusions

Chemonucleolysis by condoliase can improve symptoms in patients with LDH who are resistant to conservative treatment without causing any serious adverse events. This treatment may be less effective for patients with a history of discectomy, spondylolisthesis, or a posterior intervertebral angle of ≥5°. Injection of condoliase seems to be most effective for trans-ligamentous type and herniation, with high signal change on the T2-weighted image.

References

1. Peul WC, van Houwelingen HC, van den Hout WB, Brand R, Eekhof JA, Tans JT, Thomeer RT, Koes BW. Surgery versus prolonged conservative treatment for sciatica. N Engl J Med 2007 May 31;356(22):2245-56.

2. Weinstein JN, Tosteson TD, Lurie JD, Tosteson AN, Hanscom B, Skinner JS, Abdu WA, Hilibrand AS, Boden SD, Deyo RA. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. JAMA 2006 Nov 22;296(20):2441-50.

3. Hansson E, Hansson T. The cost-utility of lumbar disc herniation surgery. Eur Spine J 2007 Mar;16(3):329-37.

4. Koenig L, Dall TM, Gu Q, Saavoss J, Schafer MF. How does accounting for worker productivity affect the measured cost-effectiveness of lumbar discectomy? Clin Orthop Relat Res 2014 Apr;472(4):1069-79.

5. Huang W, Han Z, Liu J, Yu L, Yu X. Risk Factors for Recurrent Lumbar Disc Herniation: A Systematic Review and Meta-Analysis. Medicine (Baltimore) 2016 Jan;95(2):e2378.

6. Fjeld OR, Grovle L, Helgeland J, Smastuen MC, Solberg TK, Zwart JA, Grotle M. Complications, reoperations, readmissions, and length of hospital stay in 34 639 surgical cases of lumbar disc herniation. Bone Joint J 2019 Apr;101-b(4):470-7.

7. Nordby EJ, Fraser RD, Javid MJ. Chemonucleolysis. Spine (Phila Pa 1976) 1996 May 1;21(9):1102-5.

8. Brown MD. Update on Chemonucleolysis. Spine 1996;21(24S):62S-8S.

9. Simmons JW, Nordby EJ, Hadjipavlou AG. Chemonucleolysis: the state of the art. Eur Spine J 2001 Jun;10(3):192-202.

10. Shields CB, Reiss SJ, Garretson HD. Chemonucleolysis with chymopapain: results in 150 patients. J Neurosurg 1987 Aug;67(2):187-91.

11. Szypryt EP, Gibson MJ, Mulholland RC, Worthington BS. The long-term effect of chemonucleolysis on the intervertebral disc as assessed by magnetic resonance imaging. Spine (Phila Pa 1976) 1987 Sep;12(7):707-11.

12. Wardlaw D. Sciatica caused by disc herniation: Why is Chymopapain Chemonucleolysis denied to our patients? Int J Spine Surg 2016;10:44.

13. Nordby EJ, Wright PH, Schofield SR. Safety of chemonucleolysis. Adverse effects reported in the United States, 1982-1991. Clin Orthop Relat Res 1993 Aug;(293):122-34.

14. Yamagata T, Saito H, Habuchi O, Suzuki S. Purification and properties of bacterial chondroitinases and chondrosulfatases. J Biol Chem 1968 Apr 10;243(7):1523-35.

15. Hamai A, Hashimoto N, Mochizuki H, Kato F, Makiguchi Y, Horie K, Suzuki S. Two distinct chondroitin sulfate ABC lyases. An endoeliminase yielding tetrasaccharides and an exoeliminase

preferentially acting on oligosaccharides. J Biol Chem 1997 Apr 4;272(14):9123-30.

16. Kato F, Mimatsu K, Iwata H, Miura T. Comparison of tissue reaction with chondroitinase ABC and chymopapain in rabbits as the basis of clinical application in chemonucleolysis. Clin Orthop Relat Res 1993 Mar;(288):294-302.

17. Matsuyama Y, Chiba K, Iwata H, Seo T, Toyama Y. A multicenter, randomized, double-blind, dose-finding study of condoliase in patients with lumbar disc herniation. J Neurosurg Spine 2018 May;28(5):499-511.

18. Chiba K, Matsuyama Y, Seo T, Toyama Y. Condoliase for the Treatment of Lumbar Disc Herniation: A Randomized Controlled Trial. Spine (Phila Pa 1976) 2018 Aug 1;43(15):E869-e76.

19. Matsuyama Y, Chiba K. Condoliase for treatment of lumbar disc herniation. Drugs Today (Barc) 2019 Jan;55(1):17-23.

20. Kamper SJ, Ostelo RW, Rubinstein SM, Nellensteijn JM, Peul WC, Arts MP, van Tulder MW. Minimally invasive surgery for lumbar disc herniation: a systematic review and meta-analysis. Eur Spine J 2014 May;23(5):1021-43.

21. Agre K, Wilson RR, Brim M, Mcdermott DJ. Chymodiactin Postmarketing Surveillance: Demographic and Adverse Experience Data in 29,075 Patients. Spine 1984;9(5):479-85.

22. Komori H, Shinomiya K, Nakai O, Yamaura I, Takeda S, Furuya K. The natural history of herniated nucleus pulposus with radiculopathy. Spine (Phila Pa 1976) 1996 Jan 15;21(2):225-9.

23. Yukawa Y, Kato F, Matsubara Y, Kajino G, Nakamura S, Nitta H. Serial magnetic resonance imaging follow-up study of lumbar disc herniation conservatively treated for average 30 months: relation between reduction of herniation and degeneration of disc. J Spinal Disord 1996 Jun;9(3):251-6.

24. Peng B, Hou S, Wu W, Zhang C, Yang Y. The pathogenesis and clinical significance of a high-intensity zone (HIZ) of lumbar intervertebral disc on MR imaging in the patient with discogenic low back pain. Eur Spine J 2006 May;15(5):583-7.

25. 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 Dec 1;25(23):2987-92.

26. Rasekhi A, Babaahmadi A, Assadsangabi R, Nabavizadeh SA. Clinical manifestations and MRI findings of patients with hydrated and dehydrated lumbar disc herniation. Acad Radiol 2006 Dec;13(12):1485-9.

27. Wardlaw D, Rithchie IK, Sabboubeh AF, Vavdha M, Downing M, Eastmond CJ. Prospective randomized trial of chemonucleolysis compared with surgery for soft disc herniation with 1-year, intermediate, and long-term outcome: part II: the radiological outcome. Spine (Phila Pa 1976) 2013 Aug 1;38(17):E1058-64.

28. Gibson JN, Grant IC, Waddell G. The Cochrane review of surgery for lumbar disc prolapse

and degenerative lumbar spondylosis. Spine (Phila Pa 1976) 1999 Sep 1;24(17):1820-32.

Figure legends

Figure 1

Representative sagittal (A) and axial (B) T2-weighted magnetic resonance images showing a high-intensity area within the protruded herniation (white arrow).

Figure 2

Bar graphs of changes in the Oswestry Disability Index (ODI) and visual analogue scale (VAS) following condoliase injection. The ODI and VAS for back and leg pain improved significantly at 3 months after injection compared with the baseline ($p < 0.01$).

Figure 3

Case 1: A 50-year-old woman.

Baseline sagittal (A) and axial (B) T2-weighted magnetic resonance images (MRI) showing sub-ligamentous herniation at L5/S. Sagittal (C) and axial (D) MRI taken 3 months after condoliase injection showing significant reduction in disc herniation.

Figure 4

Case 2: A 68-year-old woman.

Baseline sagittal (A) and axial (B) T2-weighted magnetic resonance images (MRI) showing trans-ligamentous herniation with high signal intensity at L4/5. Sagittal (C) and axial (D) MRI taken 3 months after condoliase injection showing significant reduction in disc herniation.

Table 1 Demographic and baseline characteristics of the patients

	All cases (n=47)	Except 5 cases required operation within 3 months
Age (years)	48.0 ± 17.7	48.6 ± 18.3
Female	20 (42.5%)	17 (40.5%)
Herniation level		
L2/3	1 (2.1%)	1 (2.4%)
L3/4	2 (4.2%)	2 (4.8%)
L4/5	23 (48.9%)	20 (47.6%)
L5/S	21 (44.7%)	19 (45.2%)
Symptom duration (months)	8 [1–60]	8 [1–60]
Muscle weakness	6 (12.8%)	5 (11.9%)
VAS for leg pain (mm)	7.1 ± 2.6	6.9 ± 2.6
VAS for back pain (mm)	5.1 ± 2.9	5.0 ± 2.8
ODI (%)	44.6 ± 20.4	42.2 ± 20.3
Spondylolisthesis (anterior/posterior)	5 (10.6%) / 7 (14.9%)	3(7.1%) / 5 (11.9%)
Posterior intervertebral angle ≥5°	5 (10.6%)	3 (7.1%)
Vertebral translation ≥3 mm	3 (6.4%)	2 (4.8%)
Herniation type		
sub-ligamentous	33 (70.2%)	29 (69.0%)
trans-ligamentous	13 (27.7%)	12 (28.6%)
Foraminal	1 (2.1%)	1 (2.4%)
High signal intensity of herniation on T2-weighted MRI	9 (19.1%)	9 (21.4%)
Pfirrmann classification		
Grade II	4 (8.5%)	3 (7.1%)
Grade III	31 (66.0%)	28 (66.7%)
Grade IV	12 (25.5%)	11 (26.2%)
Disc height (mm)	8.0 ± 2.3	8.1 ± 2.3

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

Table 2 Comparison of demographic and baseline characteristics of groups E and I

	Group E (n = 33)	Group I (n = 14)	p-value
Age (y)	47.9 ± 18.8	48.2 ± 15.7	0.962
Female	12 (36.4%)	8 (57.1%)	0.188
Herniation level			
L2/3	1 (3.0%)	0	
L3/4	1 (3.0%)	1 (7.1%)	
L4/5	16 (48.5%)	7 (50.0%)	
L5/S	14 (42.4%)	7 (50.0%)	
History of discectomy at the same level	0	3 (21%)	**0.016***
Symptom duration (months)	6 [1–60]	12 [1–36]	0.270

Continuous data are presented as mean ± standard deviation or median [range]. Categorical data are presented as number (%). Abbreviations: E, efficacious group; I, inefficacious group.

*p<0.05 Fisher's exact test

Table 3 Comparison of imaging findings between groups E and I

	Group E (n = 33)	Group I (n = 14)	p value
Spondylolisthesis			
anterior	2 (6.0%)	3 (21.4%)	0.148
posterior	3 (9.1%)	4 (28.6%)	0.105
total	5 (15.2%)	7 (50.0%)	**0.018***
Posterior intervertebral angle ≥5°	1 (3.0%)	4 (28.6%)	**0.023***
Vertebral translation ≥3 mm	1 (3.0%)	2 (14.3%)	0.208
Herniation type			
Sub-ligamentous	20 (60.6%)	13 (92.9%)	**0.026***
Trans-ligamentous	12 (36.4%)	1 (7.1%)	**0.039***
Foraminal	1 (3.0%)	0	0.702
High signal intensity of herniation on T2-weighted MRI	9 (27.3%)	0	**0.028***
Pfirrmann classification			
Grade II	2 (6.0%)	2 (14.3%)	0.342
Grade III	22 (66.7%)	9 (64.3%)	0.565
Grade IV	9 (27.3%)	3 (21.4%)	0.489

Data are presented as number (%). Abbreviations: E, efficacious group; I, inefficacious group, MRI, magnetic resonance imaging.

*$p<0.05$ Fisher's exact test

Table 4 A comparison of magnetic resonance imaging changes between groups E and I

	Total patients (n = 42)	Group E (n = 33)	Group I (n = 9)	p-value
Disc height decrease ≥20%	15 (35.7%)	14 (42.4%)	1 (11.1%)	0.085
Progression of Pfirrmann grade	18 (42.9%)	16 (48.5%)	2 (22.2%)	0.151
Reduction of herniation	26 (61.9%)	24 (72.7%)	2 (22.2%)	**0.009***

Data are presented as number (%). Abbreviations: E, efficacious group; I, inefficacious group.

*$p<0.05$ Fisher's exact test

In this table we exclude 5 cases required operation within 3 months from Group I.

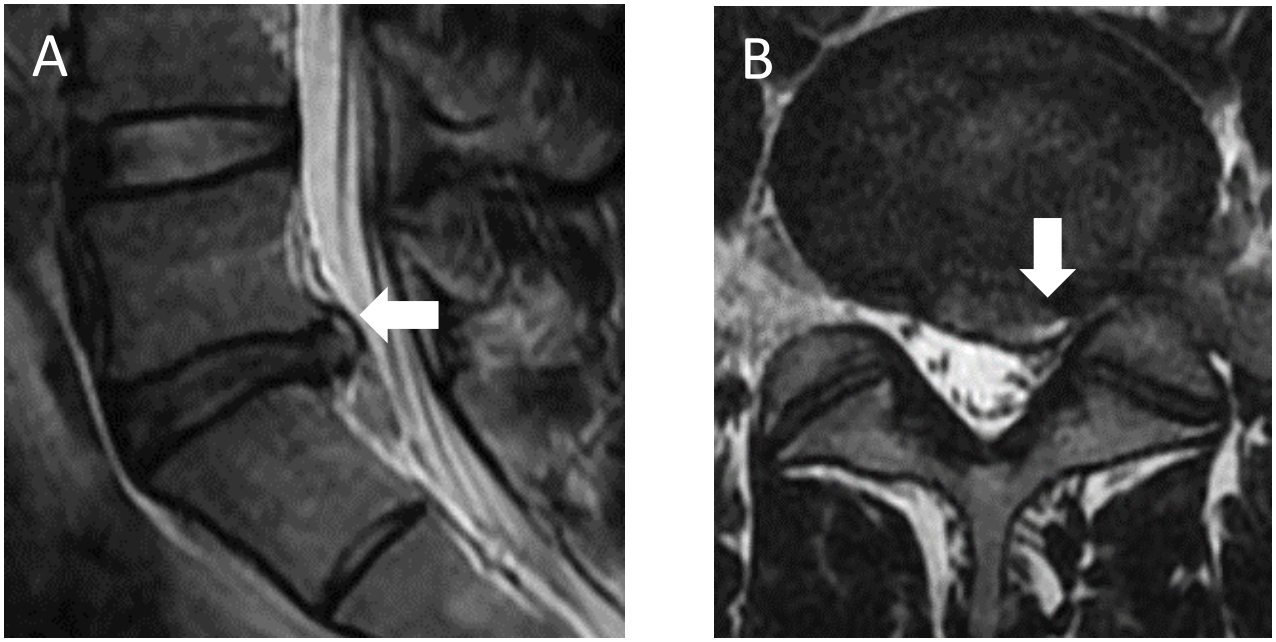
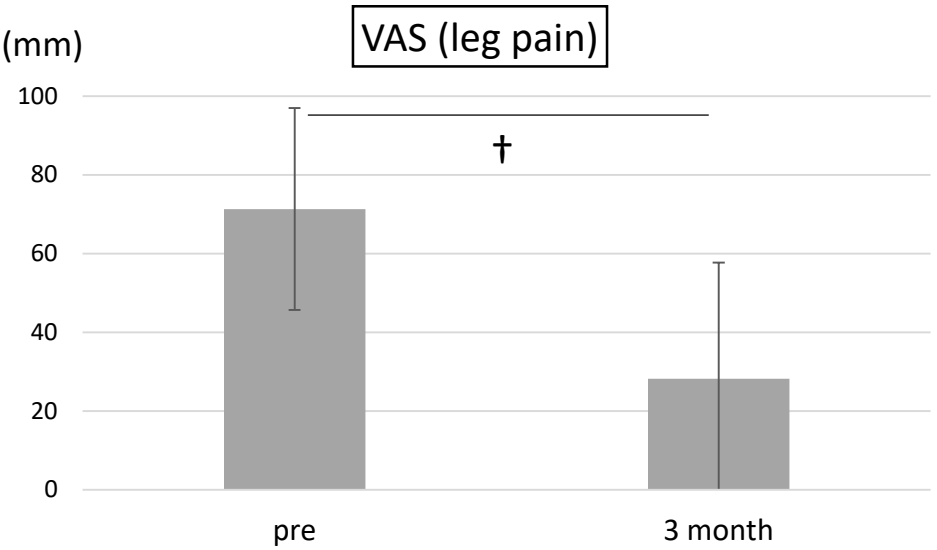
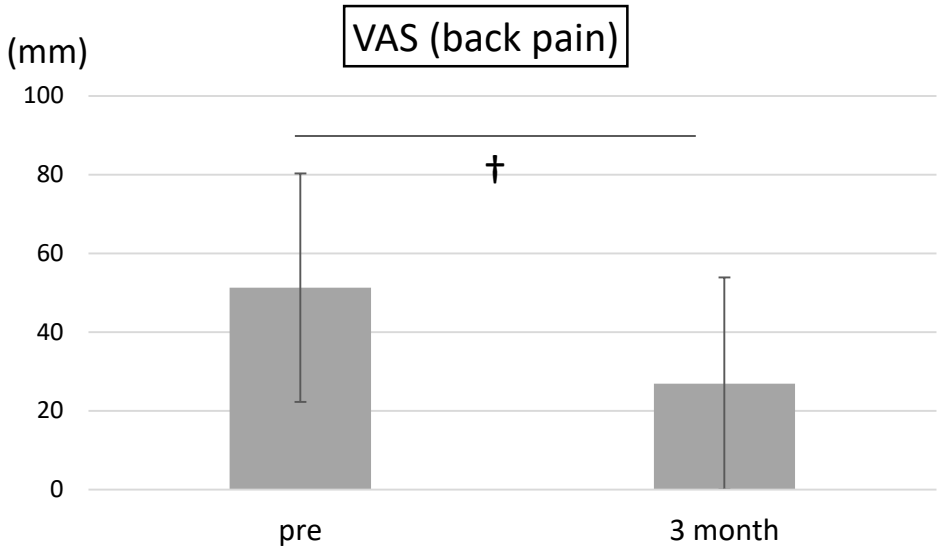
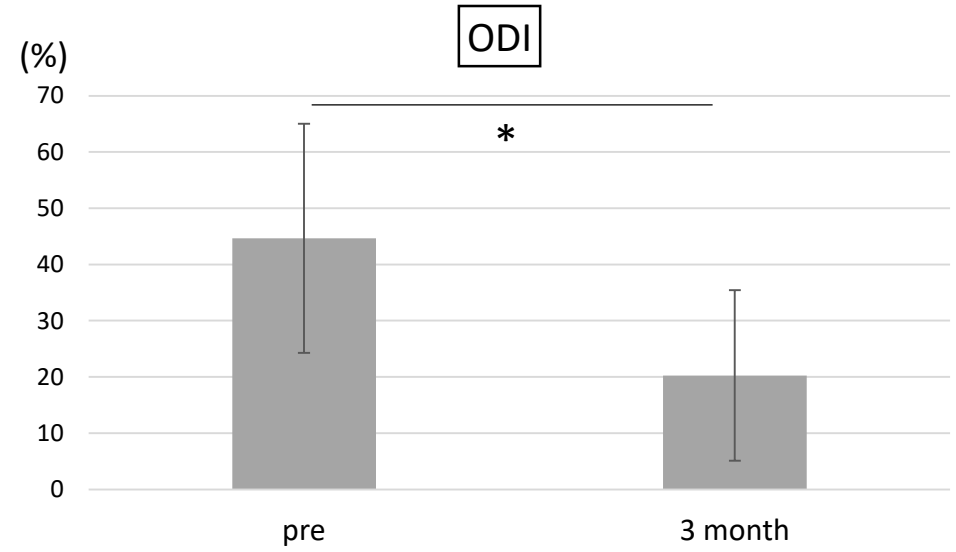


Figure 1







* p<0.01 paired t-test

† p<0.01 Wilcoxon signed-rank test

Figure 2

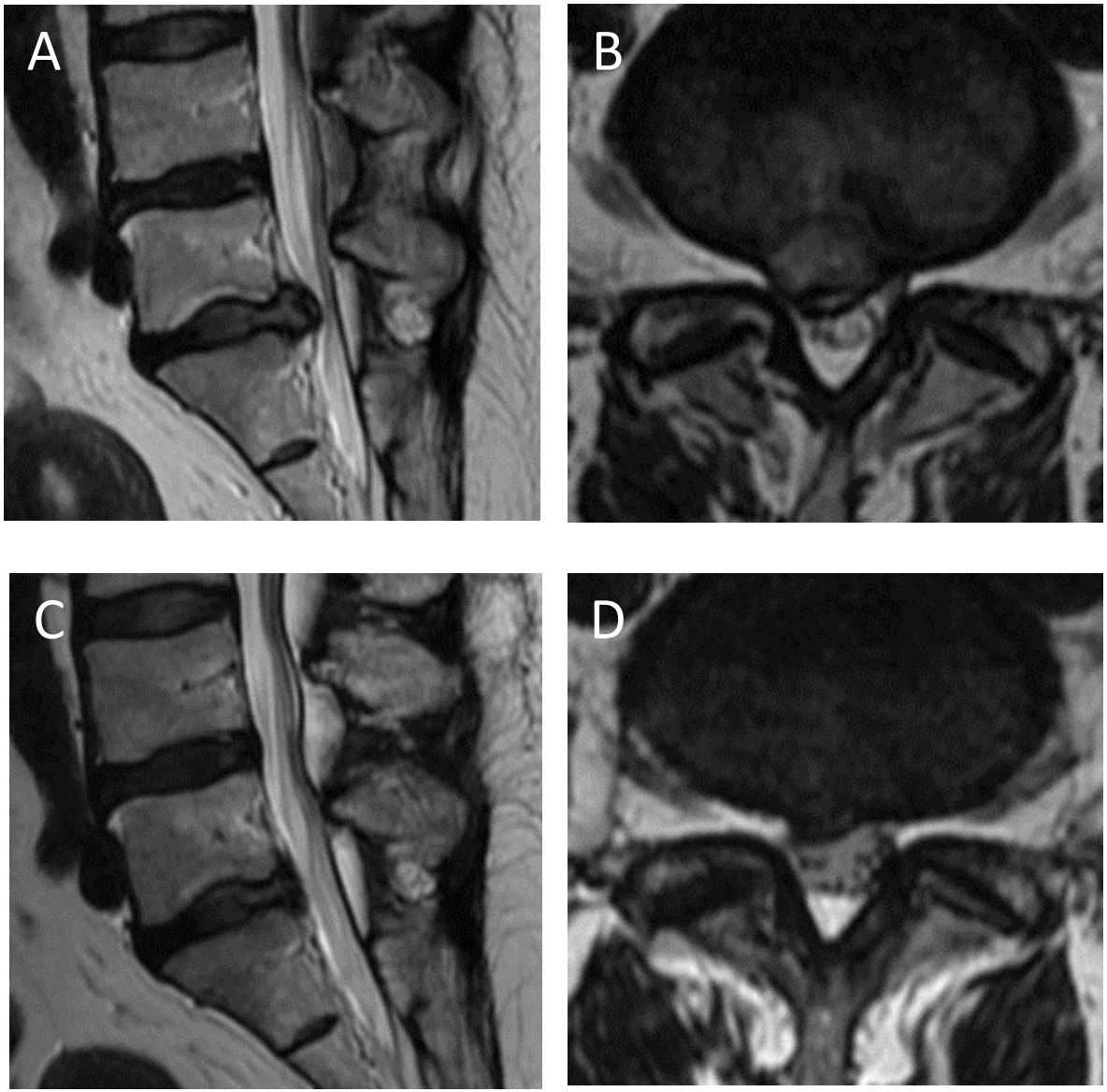


Figure 3

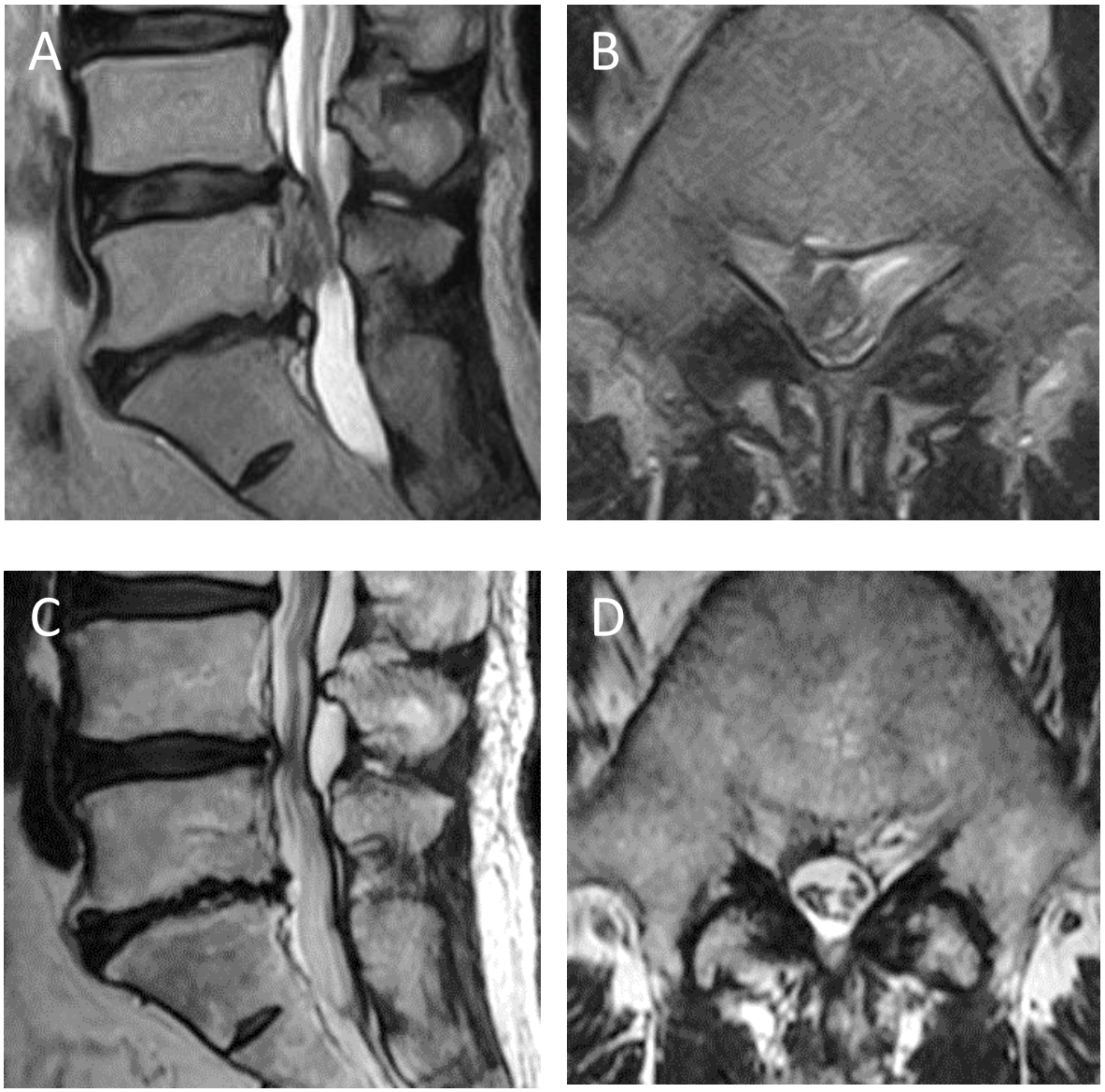


Figure 4