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The Efficacy of Condoliase for Treatment of Lumbar Disc Herniation: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Lumbar disc herniation (LDH) results in significant daily activity restriction and morbidity. Even though 90% of patients initially respond well to conservative measures, complex and costly surgical procedures are sometimes indicated in certain patients. As a relatively novel treatment for LDH, Condoliase (chondroitin sulfate ABC endolyase) offers the capability to serve as a safe and effective chemonucleolysis agent for this condition. However, there is no consensus yet to objectively describe the efficacy of this treatment.
Objectives: To compare the efficacy and safety of Condoliase vs placebo for the treatment of lumbar disc herniation.
Methods: A meta-analysis was conducted based on PRISMA guidelines. We thoroughly searched Pubmed, ProQuest, and Cochrane Library from inception up to March 2023. A total of two studies were included, divided into 7 meta-analyses, analyzed using Review Manager 5.4 software.
Results: Condoliase improves ODI score (MD 5.62 [7.97,-3.27]; $p<0.001$; $I^2=95\%$), hernia volume (MD 99.77 [65.38, 134.17]; $p<0.001$; $I^2=95\%$), and intervertebral disc volume (MD -1238.32 [-1397.34, -1079.31],$p<0.001$; $I^2=96\%$) better than placebo. There was no difference in change of worst backpain, SF-36, and adverse effect between groups.
Conclusion: Condoliase is able to improve ODI scores and pathologic changes in lumbar disc herniation compare to placebo. The adverse effect of condoliase is similar with placebo. More RCT study is needed to validate this finding.

Keywords: *condoliase, placebo, lumbar disc herniation*

INTRODUCTION

Lumbar disc herniation (LDH) is a leading cause of lower back pain, resulting from the displacement of the nucleus pulposus or annulus fibrosus beyond the boundaries of the intervertebral disc space. The estimated prevalence of symptomatic LDH is about 1-3% and it most frequently affects individuals between their 30s and 50s.[1] Lumbar disc herniation may result in significant daily activity restriction and reduced quality of life.[2] The management of LDH can be either surgically or conservatively. Approximately 90% of patients initially respond favorably to conservative measures.[3] Chemonucleosis is

one of the non-surgical therapies for LDH that includes injecting an enzyme into the nucleus pulposus of the vertebral disc to dissolve the inner portion of the disc.[4–6] Chemonucleolysis with chymopapain, an enzyme from the papaya fruit, was popular in 1980 in Western countries. Nevertheless, chymopapain was removed from the market in early 2003 due to potential adverse effects such as anaphylactic reaction and neurologic deterioration.[7,8]

Several clinical trials have shown the superior efficacy of Condoliase compared to placebo.[12,13] The use of Condoliase as chemonucleolysis agent for LDH treatment has been authorized by Japanese government in 2018, but the consensus in other country was still limited. There is no meta-analysis yet to conclude the evidence regarding the safety and efficacy of this management. Thus, the objective of this study was to assess the efficacy and safety of condoliase compared to placebo for treating lumbar disc herniation.

MATERIALS & METHODS

This systematic review and meta-analysis was conducted following the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol.

Search Strategy and Study Selection

A comprehensive search was conducted across PubMed, ProQuest, the Cochrane Library, and ClinicalTrials.gov from their inception through January 2023. The keywords used during literature searching were as follows: ("Condoliase" OR "chondroitin sulfate ABC endolyase"), ("lumbar disc herniation" OR "low back pain" OR "herniated disc" OR "disc herniation"). We included all studies regarding the effect of Condoliase vs placebo. The inclusion criteria were as follows: 1) original study, 2) reporting the comparison of Oswestry Disability Index (ODI score), worst backpain, SF-36, hernia volume, intervertebral disc space, or adverse effect between groups. We excluded study that are performed in non-human subject, published in non-English language, unaccessible fulltext, case reports, case series, letters to editor, editorials, and review article.

Quality Assessment and Extracted Data

The risk of bias in randomized controlled trials (RCTs) was assessed using the Cochrane Risk of Bias Tool for Randomized Trials version 2 (RoB 2), while non-randomized studies were evaluated using the Newcastle-Ottawa Scale (NOS). The extracted data including author's name, publication year, study design, sample size, ODI score, worst backpain, SF-36 score, hernia volume, intervertebral disc space, and the adverse event in Condoliase group and in placebo group.

Data Analysis

All statistical analyses were conducted using Review Manager® (RevMan) version 5.4 for Windows (Cochrane Collaboration, Oxford, UK). Heterogeneity was evaluated using the I^2 statistic. If sample heterogeneity was low ($I^2 < 50\%$), a fixed-effects model would be used for the analysis. If heterogeneity was high ($I^2 \geq 50\%$), then a random-effects model would be used. Continuous data was presented using Standardized Mean Differences (SMD) while dichotomous data was presented using Pooled Odds Ratio and 95% confidence intervals.

RESULTS

The initial literature search using predetermined keywords found a total of 371 studies. After checking for duplication, 26 duplicate studies were removed and 326 records were marked as ineligible. Screening based on title and abstracts excluded 4 studies due to various reasons. Sixteen studies had full-text available and were assesses for eligibility. Four studies met the inclusion criteria for the systematic review, and two were included in the meta-analysis. The flow chart of study selection is illustrated in Figure 1.

Study Characteristics

A total of four studies were included in this systematic review, with two of them incorporated into the meta-analysis. The included studies consisting of two randomized controlled trials (RCT), one retrospective study, and one prospective study. All studies were conducted in Japan. A total of 541 patients with LDH were involved, with a minimum follow-up of 3 months and the longest follow-up was 52 weeks. The studies were published from 2018-2023. Study characteristics were shown in Table 1. Condoliase injection was able to improve VAS, numbness, JOA, ODI, and disc height at 4 weeks in LDH patients compared to before injection.[11] Condoliase was effective for both lateral LDH and medial LDH.[14] Outcome Comparison of Condoliase injection versus Placebo were shown in Table 2.

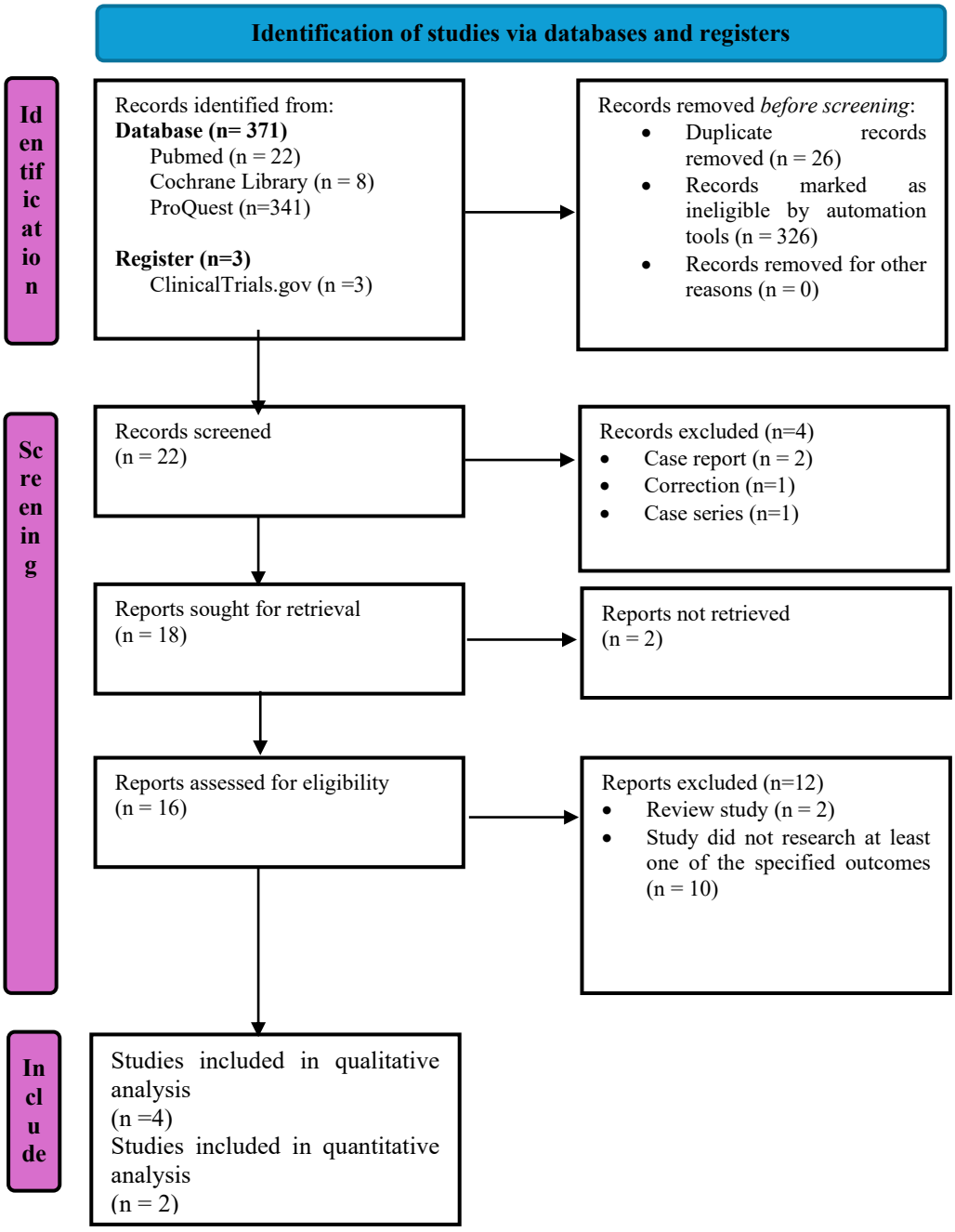

Figure 1. Flow chart of study selection

Table 1. Study Characteristics

Study	Dosage	Inclusion Critera	Design	Samples	Sample Age (years)	Follow-up	Measuring Instrument	Result
Chiba et al., 2018[12]	1.25 U	Participants aged 20–70 years with unilateral leg pain, a positive straight leg raise (SLR) test, and contained lumbar disc herniation (LDH) confirmed by MRI; exhibiting neurological signs corresponding to the affected nerve root; showing no improvement after at least 6 weeks of conservative treatment; and reporting a mean Visual Analog Scale (VAS) score of ≥50 mm for worst leg pain over seven consecutive days.	Multi-center phase III RCT	Condoliase: 82 Placebo: 81	Condoliase: 39.5 ± 11.1 Placebo: 39.2 ± 12.4	52 Weeks	Change in Worst back pain, ODI, SF-36, hernia volume, Intervertebral disc volume, disc height	Significant improvement in back pain, ODI, SF-36, hernia volume, Intervertebral disc volume, and disc height in Condoliase group compared to placebo.
Matsuyama et al., 2018[13]	1.25, 2.5, and 5 U	Patients aged 20–70 years presenting with unilateral leg pain and a positive straight leg raise (SLR) test, having contained lumbar disc herniation (LDH) confirmed by MRI, neurological findings consistent with the distribution of compressed nerve roots, no clinical improvement after ≥6 weeks of conservative treatment, and a mean Visual Analog Scale (VAS) score of ≥50 mm for the worst leg pain over seven consecutive days	Multi-center RCT	Condoliase: 49 Placebo: 47	Condoliase: 41.9 ± 10.9 Placebo: 34.0 ± 10.2	52 Weeks	Change in Worst back pain, ODI, SF-36, hernia volume, intervertebral disc volume, disc height	Improved change in Worst back pain, ODI, SF-36, hernia volume, intervertebral disc volume, disc height in 1.25 U Condoliase vs placebo The recommended clinical dose of condoliase is 1.25 U.
Kagami et al., 2023[14]	1.25 U	Patients over 18 years of age with unilateral leg pain and neurological signs consistent with nerve root compression as confirmed by MRI	Single-center retrospective study	24 LLDH 133 Medial MLDH	64.1 ± 13.1 years in LLDH 50.6 ± 16.7 years in MLDH	3-12 months	VAS, JOA, disc height improvement, adverse event	VAS, JOA, disc height improvement, and adverse event in lateral LDH did not differ from medial LDH Effectivity in LLDH: 75% Effectivity in MLDH: 77.4%

								(p=0,80)
Inoue et al., 2021[11]	Not stated	Sub-ligamentous extrusion type LDH, pain after > 6 weeks of conservative therapy, completed at least 6 months of follow-up	Multicenter, prospective observational study	84	4.2 ± 17.1 years old	≥ 6 months	VAS, Numbness, JOA, ODI, dis height improvement, adverse event	VAS, numbness, JOA, ODI significantly improved and disc height decreased at 4 weeks after injection compared to before injection. A total of 11 patients underwent herniotomy because of insufficient therapeutic effects. Treatment effectivity: 77.4%. Most effective injection at L5/S1.

Table 2. Outcome Comparison of Condoliase injection versus Placebo

Study	**Change in Worst back pain**		**ODI**		**Adverse effect**		**SF-36**		**Hernia Volume**		**Intervertebral Disc Vol**		**Disc Height**	
	C	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**	**C**	**P**
Chiba et al., 2018	−34.0 ±2	−24.5±3	−23.2 ±2	−16.4 ±2	6 (7.3%)	7 (8.64%)	PCS: 16.1±1.8 MCS: 3.2±0.9	PCS: 6.1 (1.0 to 11.1) MCS: 1·3 (−1·1 to 3·8)	−456.2 ± 30.9	−33.1 ± 31.2	12.0± 4.2	12.3±4.3	0.26±0.05	0.27±0.06
et al., 2018 (comparad to 1.25 U group)	−31.4 ±3.5	−21.1 ±3.6	41.6± 15.4	39.0 ±14.3	38 (77.6%)	35 (74.5%)	PCS: 18.2 ±16.3 MCS: 24.5 ±12.3	PCS: 46.9±8.7 MCS: 44.8 ±9.8	1.49 ±0.52	1.39 ±0.51	14.66 ±3.70	13.30±3.70	0.259± 0.060	0.259±0.042

***C : Condoliase; P : placebo ; PCS : Physical Component Score ; MCS : Mental Component Score**

Risk of Bias Assessment

The risk of bias assessment for the randomized controlled trials (RCTs) indicated predominantly low risk, with some concerns regarding attrition and reporting bias (Figure 2). For non-randomized studies, the risk of bias was low across all included studies (Table 3).

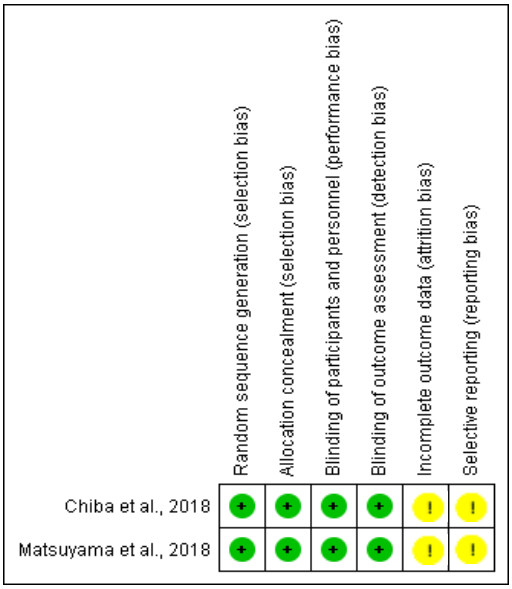

Figure 1. Risk of Bias Assessment

Table 3. Risk of Bias Assessment for non-randomized studies

Study	Selection	Comparability	Exposure	Total Star
Kagami et al., 2023	****	**	**	8 (low risk)
Inoue et al., 2021	****	**	**	8 (low risk)

Efficacy of Condoliase vs Placebo

The efficacy of condoliase vs placebo for LDH treatment was shown in Figure 3-Figure 8). Condoliase improves ODI score (MD -2.41 [11.6,6.78]; p<0.001; I^2=95%), hernia volume (MD -0.05 [-2.59, 2.50]; p<0.001; I^2=95%), and intervertebral disc volume (MD 0.76 [-0.22, 1.74], p<0.001; I^2=96%) better than placebo. There was no difference in change of worst backpain and SF-36 between groups.

Safety of Condoliase vs Placebo

The adverse effect between condoliase vs placebo was comparable (OR 1.12 [0.41, 3.11]; p=0.28; I^2=15%). The forest plot of adverse effect between condoliase vs placebo was shown in Figure 9. Matsuyama et al.[13] reported that in the condoliase groups, 10 patients had severe adverse events (AEs) that either went away or got better. In a study by Chiba et al.[12], it is concluded that 4 patients had adverse effect in week 13. Meanwhile in a study by Inoue et al.[11], three cases of adverse events following condoliase administration were reported. There was no adverse event found in study by Kagami et al.[14]

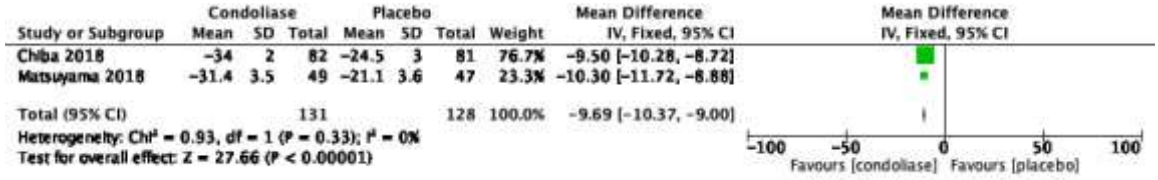

Figure 2. Change in Worst Back Pain

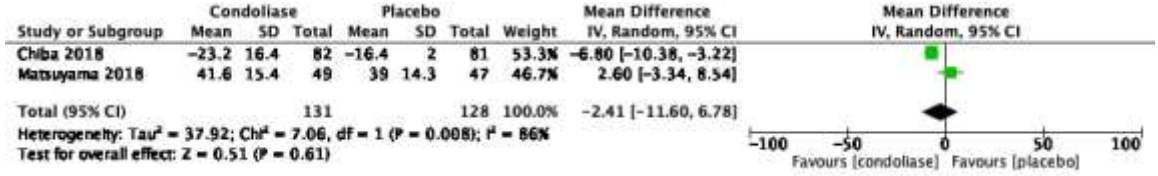

Figure 3. Change in ODI score

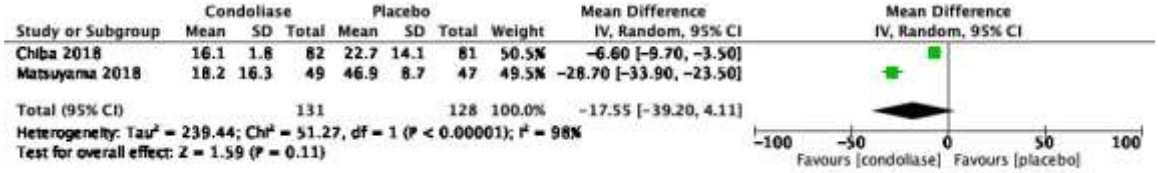

Figure 4. Change in SF-36 PCS

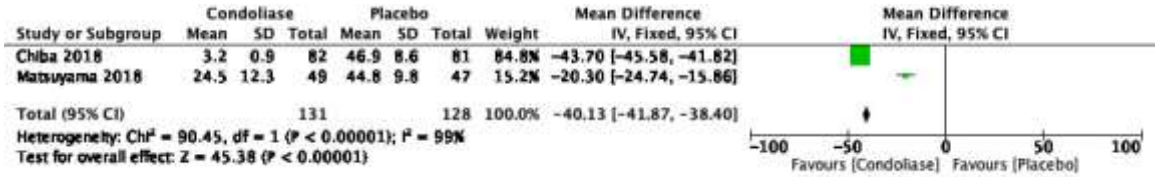

Figure 5. Change in SF-36 MCS

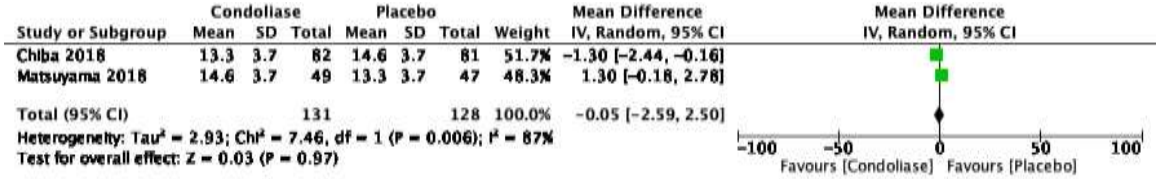

Figure 6. Change in hernia volume

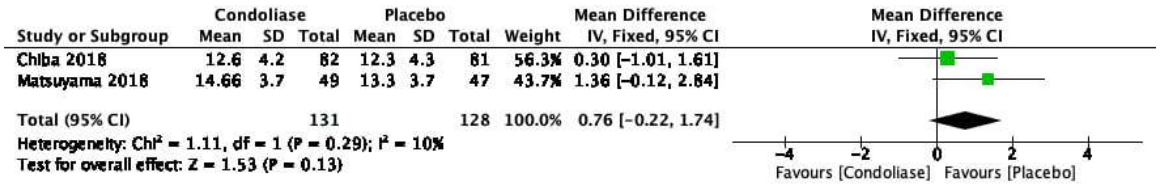

Figure 7. Change in intervertebral disc volume

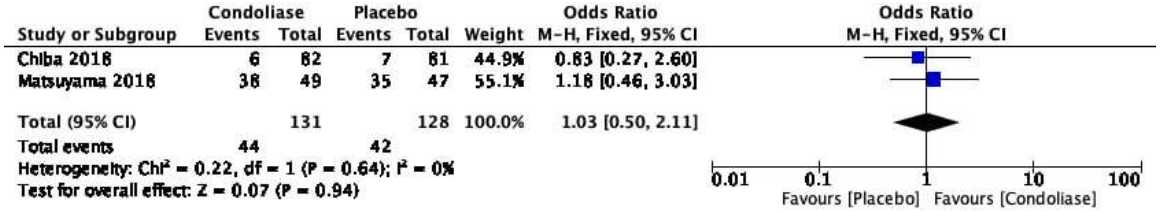

Figure 8. Adverse effect Rate

DISCUSSION

This is the first systematic review and meta-analysis evaluating Condoliase as a treatment for lumbar disc herniation (LDH) and comparing its efficacy and safety against placebo. The findings in this study were Condoliase was able to improve ODI scores and pathologic changes including hernia volume and intervertebral disc volume in lumbar disc herniation compare to placebo. There was no difference in change of worst backpain, SF-36, and adverse effect between groups. The optimal dose for Condoliase injection was 1.25 U, the most effective site administration was at L5-S1, and Condoliase was equally effective for medial and lateral LDH.[13,14]

Condoliase is a glycosaminoglycan-degrading enzyme that is derived from gram-negative *Proteus vulgaris* bacteria. Condoliase mechanism of action is by break down glycosaminoglycan in nucleus pulposus, therefore reducing intradiscal pressure, release the nerve root compression, and improve LDH symptoms.[13] Condoliase was found to be selective for chondroitin sulfate which are abundant in glycosaminoglycan in nucleus pulposus.[15] Different from chymopapain, Condoliase has no protease activity, therefore will not destroy the adjacent structure other than nucleus pulposus in the vertebral disc.[9–11]

Condoliase injection was found to be more effective when being administered at L5-S1 disk level due to the larger hernia mass in L5-S1 compared to other level.[11] Intradiscal injection of condoliase appears to be most effective in patients with larger herniated disc volumes, while showing less efficacy in those with milder intervertebral disc degeneration and longer symptom duration.[15]

There are several advantages of Condoliase injection for LDH treatment. First, it is a minimally invasive treatment. Condoliase can be performed as an outpatient procedure, with minimal trauma and pain to the patient. It can save inpatient medical expenditures and offer advantages including faster return to work, smaller wounds, and shorter duration of treatment-related discomfort.[16] Chemonucleolysis with Condoliase can be an alternative for patient who is unable or not willing to do surgery. It can be performed in patients who failed previous conservative treatments and the patients had possibility to avoid surgery. Cost-effectiveness analysis of Condoliase revealed that even failed Condoliase that was followed by open or laparoscopic surgery was cheaper than early surgery in the beginning. Condoliase was also proved to be a cost-effective options compared to conservative treatment.[16] Condoliase was applicable for many types of LDH, including transligamentous extrusion-type, subligamentous extrusion-type, lateral type, posterior disc angle, and revision cases.[14,17] However, only one Condoliase procedure is allowed per lifetime to prevent anaphylactic reaction.[8,15]

This study showed that there is an improvement of ODI score in Condoliase injection group compared to placebo. Oswestry Disability Index (ODI) is one of the most frequent methods for evaluating the symptoms and severity of low back pain. It is a patient-reported outcome questionnaire consisting of 10 items. Higher scores on the Oswestry questionnaire indicate greater levels of perceived disability.[18]

Study by Inoue et al that compare the efficacy before and after Condoliase injection showed that there was a pain reduction by more than 50% in 77.4% patient after 6 months follow-up. The pain was started to alleviate at 1-2 weeks after injection, continued to be improved over time, and almost completely disappeared at 6 months.[11] In surgery, previous RCT revealed that the pain was relieved four weeks after lumbar disk herniotomy. Early surgery was found to provide faster relief from pain, but the result were similar after one year.[19]

Though pain reduction process is said to be more slowly in condoliase treatment compared to surgery, but surgery was avoidable in up to 87% patients failing to respond to previous conservative measures. Cautions should be taken when treating patients with history of previous spine surgery, spondylolisthesis, and posterior intervertebral angle <5 degrees as these conditions are associated with less efficacy. Due to decreased intervertebral disc pressure, disc height might also be reduced, increasing potential for nerve root compression in patients with large hernia mass and prior foraminal stenosis.[11]

The strength of this study is the first meta-analysis investigating the efficacy of Condoliase as the treatment of LDH. Both of the analyzed studies in this meta-analysis have similar inclusion criteria and exclusion

criteria. This study also highlighted the optimal dose for Condoliase injection which is 1.25 U and that Condoliase can be used for medial and lateral LDH. However, this study has several limitations. First, there is only few studies available and all study were conducted in Japan, therefore the demographic characteristics was limited. Studies conducted in other country with the other ethnicity are urgently needed. The drop-out rate in both groups were quite high with unclear reason that need to be investigated.

Finally, this study conclude that Condoliase is able to improve ODI scores and pathologic changes in lumbar disc herniation compare to placebo. The adverse effect of condoliase is similar with placebo. To support this conclusion, further RCT research is required, particularly in Japan's outside regions.

CONCLUSION

Condoliase is able to improve functional outcome and pathologic changes in lumbar disc herniation compare to placebo, with similar adverse effect rate.

Declaration by Authors

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Conflict of Interest: The authors declare that the study was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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