Korean J Pain 2021;34(3):346-368
https://doi.org/10.3344/kjp.2021.34.3.346
pISSN 2005-9159 eISSN 2093-0569

KJP

Clinical Research Article

Check for updates

The role of percutaneous neurolysis in lumbar disc herniation: systematic review and meta-analysis

Laxmaiah Manchikanti[1], Emilija Knezevic[2], Nebojsa Nick Knezevic[3], Mahendra R. Sanapati[1], Alan D. Kaye[4], Srinivasa Thota[1], and Joshua A. Hirsch[5]

[1]*Pain Management Centers of America, Paducah, KY & Evansville, IN, USA*
[2]*University of Illinois at Urbana-Champaign, College of Liberal Arts and Sciences, Champaign, IL, USA*
[3]*Advocate Illinois Masonic Medical Center and College of Medicine, University of Illinois, Chicago, IL, USA*
[4]*LSU Health Sciences Center, Shreveport, Ochsner Shreveport Hospital and Pain Clinic Feist-Wieller Cancer Center, Shreveport, LA, USA*
[5]*Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA*

Received April 30, 2021
Revised May 27, 2021
Accepted May 28, 2021

Handling Editor: Kyung Hoon Kim

Correspondence
Laxmaiah Manchikanti
Pain Management Centers of America, 67 Lakeview Drive, Paducah, Kentucky 42001, USA
Tel: +1-270-554-8373, ext. 4101
Fax: +1-270-554-8987
E-mail: drlm@thepainmd.com

Background: Recalcitrant disc herniation may result in chronic lumbar radiculopathy or sciatica. Fluoroscopically directed epidural injections and other conservative modalities may provide inadequate improvement in some patients. In these cases, percutaneous neurolysis with targeted delivery of medications is often the next step in pain management.
Methods: An evidence-based system of methodologic assessment, namely, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) was used. Multiple databases were searched from 1966 to January 2021. Principles of the best evidence synthesis were incorporated into qualitative evidence synthesis. The primary outcome measure was the proportion of patients with significant pain relief and functional improvement (≥ 50%). Duration of relief was categorized as short-term (< 6 months) and long-term (≥ 6 months).
Results: This assessment identified one high-quality randomized controlled trial (RCT) and 5 moderate-quality non-randomized studies with an application of percutaneous neurolysis in disc herniation. Overall, the results were positive, with level II evidence.
Conclusions: Based on the present systematic review, with one RCT and 5 non-randomized studies, the evidence level is II for percutaneous neurolysis in managing lumbar disc herniation.

Key Words: Catheterization; Epidural Space; Evidence-Based Medicine; Intervertebral Disc Displacement; Low Back Pain; Meta-Analysis; Observational Study; Pain Management; Radiculopathy; Randomized Controlled Trial; Saline Solution, Hypertonic; Systematic Review.

INTRODUCTION

Chronic lumbar radicular pain or sciatica may be due to a multitude of reasons including disc herniation, spinal stenosis, and post-lumbar surgery syndrome [1]. There has been extensive literature since the initial description of disc herniation by Mixter and Barr in 1934 [2]. Symptomatic herniated lumbar disc was shown to be present in 1% to 3% [3], whereas the highest prevalence was among people aged 30 to 50 years [4]. Further, herniated discs occurred

Author contributions: Laxmaiah Manchikanti: Study conception; Emilija Knezevic: Formal analysis; Nebojsa Nick Knezevic: Study conception; Mahendra R. Sanapati: Writing/manuscript preparation; Alan D. Kaye: Writing/manuscript preparation; Srinivasa Thota: Writing/manuscript preparation; Joshua A. Hirsch: Study conception.

most commonly at the lower lumbar spine (L4/5 and L5/S1 levels) and also among those aged 25 to 55 years [5,6].

The mechanism of radicular pain in disc herniation may relate to mechanical compression or inflammation [1,7-10]. While surgical interventions are considered the mainstay of treatment for lumbar disc herniation or radiculopathy [11], multiple studies have shown epidural injections to be effective [1,10].

Epidurals with local anesthetics, with or without steroids, performed under fluoroscopic guidance, have been shown to be effective in managing disc herniation and radiculitis in multiple studies with level I evidence [1,10]. However, the failure of epidural injections may range from 30% to 50% of patients on a long-term basis. In such cases, percutaneous neurolysis may be employed in the nonsurgical management of chronic lumbar radicular pain [1,12].

Percutaneous neurolysis has been described to treat post-lumbar surgery syndrome and central spinal stenosis; however, systematic evaluations of effectiveness are lacking with disc herniation and chronic radicular pain [1,12-17]. Percutaneous neurolysis, epidural lysis, or lysis of epidural adhesions has been utilized for the past 30 years [1,12-17]. Epidural neurolysis is based on several premises, including that epidural fibrosis may present with low back pain and/or radicular pain, not only in post-surgical syndromes and spinal stenosis, but also disc displacements with leakage of disc materials. These adhesions can cause pain by immobilizing the nerve roots and also prevent injected materials from reaching the intended targets in the epidural space. As a result, pain relief can be achieved by removing these adhesions with the adhesiolysis (neurolysis) procedure that facilitates therapeutic medications reaching the target site and restores the normal movement of the nerve roots [1,12-16,18-25]. McCarron [20] showed that the nucleus pulposus produces local inflammation and scarring in the epidural space in dogs. Further, in humans, microstructural defects accumulate over time with age, and the nucleus pulposus protrudes deeper into the annulus, resulting in tears of the annulus and disc material leaking into the epidural space [21]. This may result in epidural adhesion formation and pain related to it, based on rich innervation of the posterior longitudinal ligament, which is an important source of back pain associated with epidural adhesions [22].

Thus, in the present investigation, we have sought to evaluate the effectiveness of percutaneous neurolysis in managing chronic lumbar disc herniation and lumbar radicular pain with a systematic review and meta-analysis.

MATERIALS AND METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [26] was used for methodological and reporting quality of the systematic review and meta-analysis. The objective was to assess the effectiveness of percutaneous neurolysis in managing chronic lumbar disc herniation and radiculopathy.

1. Inclusion criteria

All randomized controlled trials (RCTs) and observational studies with inclusion of patients with chronic disc herniation, undergoing percutaneous neurolysis with caudal, lumbar interlaminar, or lumbar transforaminal approaches were considered.

2. Outcome measures

The proportion of patients with significant (≥ 50%) pain relief and improvement in function was the primary outcome.

3. Data sources

All available studies in the English language, or with available translation, with appropriate reporting of outcomes data for 6 months were included. Searches were performed using multiple databases, including PubMed (www.ncbi.nlm.nih.gov/pubmed); the Cochrane Library (www.thecochranelibrary.com); the US National Guideline Clearinghouse (www.guideline.gov/); clinical trials (www.clinicaltrials.gov/); and Google Scholar (https://scholar.google.com) from 1966 to January 2021.

4. Search strategy

The search terminology was as follows:
((((((((((((((((chronic low back pain) OR nerve root compression) OR lumbosciatic pain) OR radicular pain) OR radiculitis) OR sciatica) OR disc herniation) AND ((((((((((epidural injection) OR epidural adhesiolysis OR neurolysis) OR epidural neuroplasty) OR epidural lysis of adhesions) OR percutaneous adhesiolysis OR neurolysis `OR transforaminal injection) OR corticosteroid) OR methylprednisolone) OR bupivacaine OR lidocaine))) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR systematic review OR randomized controlled trials [mh] OR nonrandomized studies OR observational studies OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw]

OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR (placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp])))).

5. Data collection and analysis

This review focused on percutaneous adhesiolysis/neurolysis for disc herniation with multiple approaches. All studies that provided appropriate outcome data and analysis for 6 months were reviewed. Book chapters, case reports, and reports without an appropriate diagnosis were not considered.

6. Inclusion criteria

Studies of interest included patients suffering from chronic lumbar radiculopathy due to disc herniation and treated with percutaneous epidural neurolysis or adhesiolysis. Studies of patients with fractures, malignancies, acute trauma, and inflammatory diseases were excluded. All RCTs and non-randomized studies with inclusion of at least 50 participants were included.

7. Data collection process

Identification of the relevant literature, the manuscript selection, and extraction of the data from the included studies was conducted independently by 2 of the review authors. Any disagreement between them was resolved by the third author. Any and all conflicts of interest of the reviewers with authorship of the manuscripts was resolved by assigning them to other reviewers.

8. Data synthesis and analysis

Two authors completed the quality assessment of each individual manuscript. Three authors completed evidence synthesis. All conflicts were resolved as stated above by a fourth author.

9. Risk of bias of individual studies

The quality of each RCT was assessed using the Cochrane review rating system (**Appendix Table 1**) [27] and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment Tool (IPM-QRB) for RCTs (**Appendix Table 2**) [28]. Non-randomized or observational studies were assessed by Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for nonrandomized or observational studies (IPM-QRBNR) (**Appendix Table 3**) [29].

Randomized trials meeting at least 9 of the 13 inclusion criteria of the Cochrane review were considered high-quality. The trials meeting 5 to 8 criteria were considered moderate-quality, and those meeting fewer than 5 criteria were considered low-quality, and were excluded.

Based on the IPM-QRB and IPM-QRBNR criteria, randomized trials and observational studies meeting scores from 32 to 48 were considered high-quality, studies scoring from 16 to 31 were considered moderate quality; and studies scoring less than 16 were considered low quality, and were excluded.

Table 1. Qualitative modified approach to grading of evidence

Level I	Strong	Evidence obtained from multiple relevant high-quality randomized controlled trials for effectiveness or Evidence obtained from multiple relevant high quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level II	Moderate	Evidence obtained from at least one relevant high-quality randomized controlled trial or multiple relevant moderate or low-quality randomized controlled trials or Evidence obtained from at least 2 high-quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level III	Fair	Evidence obtained from at least one relevant high-quality nonrandomized trial or observational study with multiple moderate or low-quality observational studies or At least one high-quality relevant observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level IV	Limited	Evidence obtained from multiple moderate or low-quality relevant observational studies or Evidence obtained from moderate quality observational studies or large case series for assessment of preventive measures, adverse consequences, and effectiveness of other measures.
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists for effectiveness as well as to assess preventive measures, adverse consequences, and effectiveness of other measures.

Adapted from the article of Manchikanti et al. (Pain Physician 2014; 17: E319-25) [30].

10. Outcome of the studies

Clinically important outcome measures of 50% significant improvement from the baseline pain score, or a change of at least 3 points on an 11-point pain scale of 0 to 10 and a change of 30% or more on disability scores.

Based on the relevance and effectiveness of the neurolysis in disc herniation, either compared to a control group or from baseline to follow-up, a study was categorized as positive or negative/neutral. Reference point measurements were considered at 3 months, 6 months, and one year.

11. Analysis of evidence

The best-evidence synthesis developed by the American Society of Interventional Pain Physicians, modified and collated using multiple criteria, was used for qualitative analysis (**Table 1**) [30]. The evidence synthesis varied from strong to opinion- or consensus-based using 5 levels of evidence.

12. Meta-analysis

Software Review Manager (Rev Man 5.3) was used (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008) for conventional or dual-arm meta-analysis. Software Comprehensive Meta-analysis version 3.0 was used (Biostat Inc., Englewood, NJ) for single-arm meta-analysis. The standardized mean differences with 95% confidence intervals were reported for pain and improvement of function data. Data were plotted by using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I^2 statistics.

RESULTS

1. Study selection

Fig. 1 shows a flow diagram of the study selection using the PRISMA study selection process [26].

Based on the search criteria, 13 manuscripts were identified and considered for inclusion [18,25,31-41]. A total of 6 studies met the inclusion criteria [25,31,33,37,38,40]. Of the 6 studies included, 2 of them [18,41] studied disc prolapse, along with post-lumbar surgery syndrome, and subgroup data analysis was not available. One study had a small sample size of 20 patients [34].

Four studies were excluded due to short-term follow-up of 6 months since less than a 3-month follow-up would not provide any long-term clinical relevance [32,35,36,39]. Of these, there was only one placebo-controlled RCT [25].

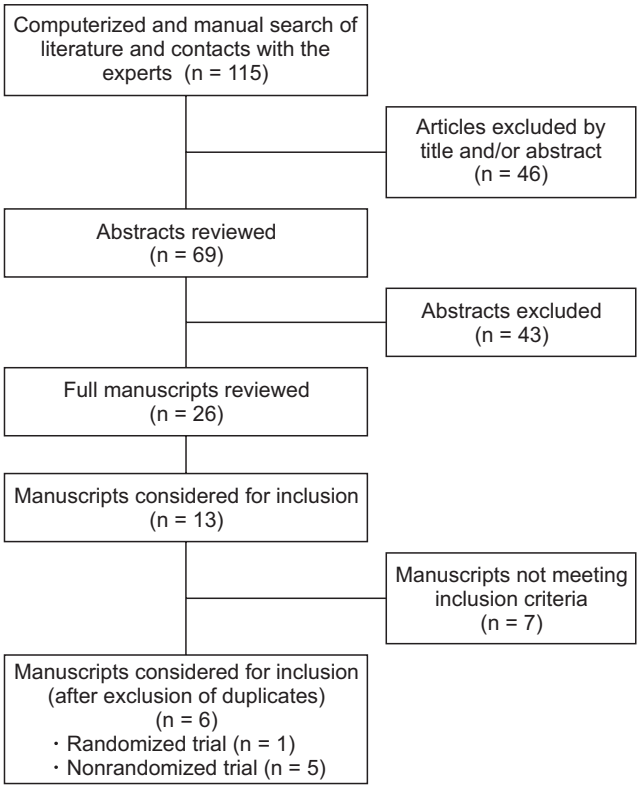


Fig. 1. Flow diagram illustrating published literature evaluating percutaneous adhesiolysis/neurolysis in lumbar disc herniation.

2. Methodologic quality and risk of bias assessment

Of the 6 manuscripts meeting inclusion criteria [25,31,33,37,38,40], there was only one placebo-controlled RCT [25]. **Appendix Tables 4 and 5** show the methodologic quality assessment and risk of bias of the one RCT utilizing the Cochrane review criteria and the IPM-QRB criteria respectively [27,28]. Assessment by the Cochrane review criteria and IPM-QRB of this RCT showed high quality [25].

Appendix Table 6 shows the assessment of the included nonrandomized or observational studies, utilizing IPM-QRBNR criteria. Five studies [31,33,37,38,40] were included. Assessment by IPM-QRBNR showed all studies to be of moderate quality.

3. Study characteristics

Table 2 shows the characteristics and outcomes of the studies meeting the inclusion criteria which involved receiving percutaneous adhesiolysis/neurolysis for lumbar disc herniation.

4. Qualitative analysis

Qualitative analysis was performed utilizing a modified

Table 2. Characteristics of included studies of percutaneous adhesiolysis/neurolysis in lumbar disc herniation

Study	Study characteristics	Methodological quality scoring	Participants and interventions	Outcome measures	Pain relief and function			Results			Comment(s)
					3 mo	6 mo	12 mo	Short-term	Long-term		
								≤ 3 mo	> 6 mo	≥ 12 mo	
Gerdesmeyer et al., 2013 [25]	RA, PC, DB Chronic lumbar radicular pain lasting longer than 4 months	Quality scores: Cochrane: 13/13 IPM-QRB 41/48	The authors screened 90 patients from 381 patients with chronic radicular pain lasting longer than 4 months over a period of 4 years. Randomization: Placebo control group = 44 • In the placebo group, a needle and catheter was inserted through caudal approach and the needle was intentionally inserted without entering the spinal canal and the catheter was inserted into the subcutaneous tissue overlying the afflicted level. • 10 mL of preservative-free sodium chloride solution was injected for 3 days and the catheter was removed. Neurolysis group = 46 • The catheter was placed through sacral canal with injection of 10 mL of contrast with identification of filling defects. Subsequently a Tun-L catheter was inserted through the epidural needle and advanced to the anterolateral area of the filling defect. • Local anesthetic, 10 mL, 0.25% bupivacaine was injected through the catheter, followed by 10 mL of preservative free sodium chloride solution containing 150 units per mL of hyaluronidase. • Sodium chloride solution, 10 mL, 10%, containing 40 mg of triamcinolone was then injected slowly, along with 2 mL of 0.25% bupivacaine. • On the 2nd and 3rd days, 10 mL of 0.25% bupivacaine was injected through the catheter, followed by slow injection of 10 mL of 10% sodium chloride solution and 2 mL, 0.25% bupivacaine. The catheter was removed on the third day in both groups.	Primary outcome measure: ODI at 3, 6, and 12 months VAS: At least 50% reduction in ODI scores and VAS scores at 3, 6, and 12 months after treatment	Placebo group = 17% (7/42) Lysis group = 58% (26/45)	Placebo group = 11% (4/37) Lysis group = 74% (31/42)	Placebo group = 35% (9/26) Lysis group = 90% (28/31)	P	P	P	This is the first true placebo controlled trial, injecting and inert substance into an inert structure, yet it showed positive response in some patients. Overall, there were significant differences in the active treatment group and lysis group compared to placebo group. Ten-year follow-up also showed significant improvement and surgery was avoided in majority of the patients. Surgery was avoided in 85% of the patients.

https://doi.org/10.3344/kjp.2021.34.3.346

Table 2. Continued

Study	Study characteristics	Methodological quality scoring	Participants and interventions	Outcome measures	Pain relief and function			Results			Comment(s)
					3 mo	6 mo	12 mo	Short-term	Long-term		
								≤ 3 mo	> 6 mo	≥ 12 mo	
Ji et al., 2015 [40]	Retrospective Lumbar disc herniation	Quality Scores: IPM-QRB-NR 30/48	Authors studied correlation of dural sac cross sectional area with a single-level disc disease and effectiveness of percutaneous epiduroplasty. Number of patients = 363 Categorization to spinal canal compromise Category 1 – less or more than 50% Category 2 – lesser than one-third, between a third and two-thirds, and more than two-thirds with subcategories • Catheterization was performed with a caudal approach. After final positioning of the Racz catheter, 6 mL of 0.2% preservative free ropivacaine containing 1,500 units of hyaluronidase and 4 mL of 40% triamcinolone acetate was injected. • One-hour after the procedure, 6 mL of 8% sodium chloride solution was infused over 30 minutes in the recovery room under monitoring. • Epidural catheter was removed.	VAS for back pain and leg pain, Odom's criteria Assessment intervals: 3, 6, 12, and 24 months	SI in VAS	SI in VAS	SI in VAS	SI in VAS	SI in VAS	SI in VAS	This study looking at dural cross sectional area in single level disc disease showed no significant difference based on dural sac cross sectional area. The results show that percutaneous epidural neuroplasty is an effective procedure in treating single-level lumbar disc herniation without affecting dural sac cross sectional area.
Moon et al., 2017 [33]	Retrospective Lumbar disc herniation	Quality Scores: IPM-QRB-NR 30/48	• 407 patients were evaluated retrospectively to predict the outcome of percutaneous epidural adhesiolysis in patients with lumbar disc herniation. • All patients underwent percutaneous adhesiolysis with an RK needle and Racz catheter through caudal approach. After final positioning of the catheter in the anterior epidural space of the target site, 3-5 mL of 1% lidocaine was administered as a test dose. This was followed by 10 mL of 0.9% sodium chloride solution, followed by injection of 0.125% bupivacaine mixed with 5 mg of dexamethasone. • After 5 minutes, 10 mL of 10% sodium chloride solution was slowly injected under real-time fluoroscopic guidance. • Catheter was removed and insertion site was sutured.	The primary outcome measure was substantial response of 4 or more points or 50% of pain relief in the numerical rate scaling pain score, 12 months after treatment. Repeat procedure was performed if needed at 3 months. Six-months not available.	NA	NA	SI in 72.2% of patients	NA	NA	P	This is a positive study with long-term follow-up assessing factors predicting favorable outcome of percutaneous epidural adhesiolysis. The presence of high intensity zone on magnetic resonance imaging was a predictor of substantial response to percutaneous epidural adhesiolysis for 12 months.

Table 2. Continued

Study	Study characteristics	Methodological quality scoring	Participants and interventions	Outcome measures	Pain relief and function			Results			Comment(s)
					3 mo	6 mo	12 mo	Short-term	Long-term		
								≤ 3 mo	> 6 mo	≥ 12 mo	
Cho et al., 2019 [31]	Retrospective Lumbar disc herniation	Quality Scores: IPM-QRB-NR 30/48	• This study included 430 consecutive patients with a single-level disc herniation undergoing percutaneous epidural neuroplasty. Authors categories LDH type as bulging, protrusion, extrusion, and sequestration. LDH type inclusion: bulging 124, protrusion 240, extrusion 56, sequestration 10, total 430. • All patients were treated with percutaneous adhesiolysis or neuroplasty through a caudal approach with placement of the catheter ventrally and laterally. Following the satisfactory positioning of the catheter and injection of contrast, 6 mL of 0.2% preservative free ropivacaine containing 1,500 units of hyaluronidase and 4 mL of betamethasone sodium phosphate was injected. • One hour after the procedure, 6 mL of 8% sodium chloride solution was infused over a period of 30 minutes under monitoring in the recovery room. Epidural catheter was removed.	VAS for back pain and leg pain, Odom's criteria with classification of outcomes as excellent, good, fair or poor. Outcomes were recorded at 1, 3, 6, and 12 months	Significant decrease in VAS scores for back and leg pain	Significant decrease in VAS scores for back and leg pain	Significant decrease in VAS scores for back and leg pain	Good or excellent outcome = 73.1	Good or excellent outcome = 74.8	Good or excellent outcome = 71.7	Overall, this is a positive study with positive results with a single treatment of one-day percutaneous adhesiolysis providing improvement in VAS of back and leg pain lasting for one-year. Surgery was avoided in more than 70% of the patients with extrusion or sequestration. Patients with Pfirrmann's Grades 1 to 3, shows a significantly higher rate of subsequent surgery than with Pfirrmann Grade 0.

https://doi.org/10.3344/kjp.2021.34.3.346

Table 2. Continued

Study	Study characteristics	Methodological quality scoring	Participants and interventions	Outcome measures	Pain relief and function			Results			Comment(s)
					3 mo	6 mo	12 mo	Short-term	Long-term		
								≤ 3 mo	> 6 mo	≥ 12 mo	
Park et al., 2018 [37]	Retrospective Lumbar disc herniation and/or spinal stenosis	Quality Scores: IPM-QRB-NR 29/48	Authors sought to evaluate clinical significance of epidurography contrast patterns after adhesiolysis. Number of patients = 78 • Both spinal stenosis and disc herniation patients were included without separating the data. • Procedure was performed with caudal entry. After appropriate positioning of the catheter, a mixture of 10 mL of 0.9% sodium chloride solution and 300 units of hyaluronidase was injected. Following this, another epidurogram was carried out. After epidurogram a mixture of 0.2% ropivacaine 8 mL and 40 mg of triamcinolone was slowly injected. • Significant improvement in VAS scores, back pain and leg pain • Significant improvement in ODI scores • Extraforaminal leakage of the contrast was associated with a tendency for decreased pain and significant better quality of life.	VAS, ODI, 12-item short-form health survey (SF-32) Outcomes assessed at 1, 3, 6, and 12 months	SI	SI	SI	P	P	P	In this study assessing clinical significance of epidurography contrast patterns, authors reported positive results and authors also showed that when there is extraforaminal contrast spread, outcomes were superior.

Table 2. Continued

Study	Study characteristics	Methodological quality scoring	Participants and interventions	Outcome measures	Pain relief and function			Results			Comment(s)
					3 mo	6 mo	12 mo	Short-term	Long-term		
								≤ 3 mo	> 6 mo	≥ 12 mo	
Choi et al., 2017 [38]	Retrospective Lumbar disc herniation and/or spinal stenosis	Quality Scores: IPM-QRB-NR 30/48	• This study included 543 patients assessing 5% or 10% hypertonic sodium chloride solution injection. • 5% group = 333 • 10% group = 210 • Procedure was performed with a caudal entry and catheterization after final catheter position was achieved. 5 mL of 0.25% ropivacaine containing 1,500 units of hyaluronidase was injected. After confirming the absence of any complications, 6 mL of 10% or 5% sodium chloride solution was injected at a rate of 1 mL every 15 minutes for 1.5 hours. This was followed by injection of 2 mL of 0.9% sodium chloride solution containing 40 mg of triamcinolone. • Epidural catheter was removed before discharging the patients	NRS	No significant differences between the groups. Both groups showed significant improvement in pain rating.	No significant differences between the groups. Both groups showed significant improvement in pain rating.	NA	P	P	NA	Short-term follow-up with positive outcomes showing no significant difference between 5% or 10% sodium chloride solution.

RA: randomized, PC: placebo control, DB: double-blind, ODI: Oswestry Disability Index, VAS: visual analog scale, SI: significant improvement, NA: not applicable, P: positive, IPM-QRB: Interventional Pain Management techniques – Quality Appraisal of Reliability and Risk of Bias Assessment, IPM-QRBNR: Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Non-randomized Studies, NRS: numeric rating scale, LDH: lumbar disc herniation.

https://doi.org/10.3344/kjp.2021.34.3.346

approach for the grading of evidence [28] with moderate (level II) evidence from one relevant high-quality RCT and 5 relevant moderate-quality observational studies. All of the studies consistently showed improvement in patients undergoing neurolysis at 6 months and one-year follow-up periods.

5. Quantitative analysis

1) Single-arm meta-analysis

Conventional dual-arm analysis was not feasible due to only one RCT being available. Consequently, single-arm meta-analysis was performed in observational studies for pain relief and functional status improvement, utilizing data from 5 studies [31,33,37,38,40].

2) 6-month follow-up

Fig. 2 shows results of the 6-month follow-up. As shown in **Fig. 2A**, there were 5 studies [25,31,37,38,40] included in this single-arm meta-analysis, and the results showed an improvement in the numeric rating scale (NRS) pain scores at 6 months after adhesiolysis/neurolysis, with an average of 2.678 ($P < 0.001$).

As shown in **Fig. 2B**, there were 2 studies [25,37] included in this single-arm meta-analysis, and the results showed an improvement in the functionality scores at 6 months after adhesiolysis/neurolysis, with an average of 9.977 (on 0-50 scale) ($P < 0.001$).

3) One-year follow-up

Fig. 3 shows results of the one-year follow-up. As shown in **Fig. 3A**, there were 5 studies [25,31,33,37,40] included in this single-arm meta-analysis, and the results showed an improvement in the NRS pain scores at 12 months after adhesiolysis/neurolysis, with an average of 2.013, which was statistically significant ($P < 0.001$).

As shown in **Fig. 3B**, there were 2 studies [25,37] included in this single-arm meta-analysis, and the results showed an improvement in the Oswestry Disability Index (ODI) functionality scores after adhesiolysis/neurolysis at 12 months, with an average of 10.268 (on 0-50 scale) ($P < 0.001$).

DISCUSSION

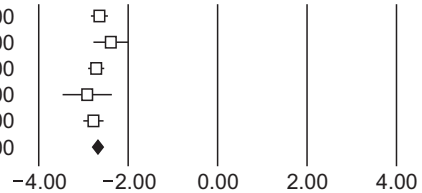
Analysis of the effectiveness of percutaneous adhesiolysis/

A

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P value
Choi et al., 2017 [38]	−2.640	0.084	0.007	−2.805	−2.475	−31.429	0.000
Gerdesmeyer et al., 2013 [25]	−2.400	0.184	0.034	−2.761	−2.039	−13.043	0.000
Cho et al., 2019 [31]	−2.700	0.082	0.007	−2.861	−2.539	−32.935	0.000
Park et al., 2018 [37]	−2.900	0.277	0.077	−3.443	−2.357	−10.469	0.000
Ji et al., 2015 [40]	−2.760	0.106	0.011	−2.967	−2.553	−26.161	0.000
	−2.678	0.049	0.002	−2.773	−2.583	−55.071	0.000

Statistics for each study

Difference in means and 95% CI



Heterogeneity				Tau-squared			
Q-value	df (Q)	P value	I-sauared	Tau squared	Standard error	Variance	Tau
3.906	4	0.433	0.000	0.000	0.009	0.000	0.000

B

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	P value
Gerdesmeyer et al., 2013 [25]	−14.500	1.438	2.068	−17.318	−11.682	−10.083	0.000
Park et al., 2018 [37]	−8.400	0.849	0.721	−10.064	−6.736	−9.894	0.000
	−9.977	0.731	0.534	−11.410	−8.544	−13.646	0.000

Statistics for each study

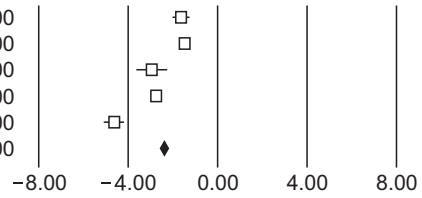
Difference in means and 95% CI

Heterogeneity				Tau-squared			
Q-value	df (Q)	P value	I-sauared	Tau squared	Standard error	Variance	Tau
13.343	1	0.000	92.506	17.211	26.311	692.292	4.149

Fig. 2. Changes in pain and functional status from baseline at 6 months. (A) Change in pain levels using the numeric rating scale from baseline at 6 months in patients treated with adhesiolysis/neurolysis. (B) Change in functionality status scores using the Oswestry Disability Index from baseline at 6 months in patients treated with adhesiolysis/neurolysis. CI: confidence interval, df: degrees of freedom.

A

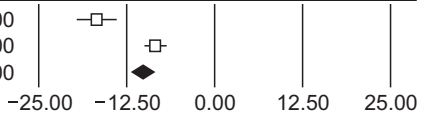
Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	*P* value
Gerdesmeyer et al., 2013 [25]	−1.600	0.184	0.034	−1.961	−1.239	−8.696	0.000
Cho et al., 2019 [31]	−1.400	0.072	0.005	−1.542	−1.258	−19.384	0.000
Park et al., 2018 [37]	−2.900	0.328	0.108	−3.543	−2.257	−8.841	0.000
Ji et al., 2015 [40]	−2.690	0.110	0.012	−2.906	−2.474	−24.455	0.000
Moon et al., 2017 [33]	−4.600	0.199	0.040	−4.990	−4.210	−23.116	0.000
	−2.013	0.054	0.003	−2.120	−1.907	−37.013	0.000



Heterogeneity				Tau-squared			
Q-value	df (Q)	*P* value	I-sauared	Tau squared	Standard error	Variance	Tau
291.116	4	0.000	98.626	1.402	1.300	1.690	1.184

B

Study name	Difference in means	Standard error	Variance	Lower limit	Upper limit	Z-value	*P* value
Gerdesmeyer et al., 2013 [25]	−16.800	1.482	2.196	−19.705	−13.895	−11.336	0.000
Park et al., 2018 [37]	−8.400	0.793	0.628	−9.953	−6.847	−10.598	0.000
	−10.268	0.699	0.488	−11.638	−8.898	−14.692	0.000



Heterogeneity				Tau-squared			
Q-value	df (Q)	*P* value	I-sauared	Tau squared	Standard error	Variance	Tau
24.981	1	0.000	95.997	33.868	49.893	2489.357	5.820

Fig. 3. Changes in pain and functional status from baseline at 12 months. (A) Change in pain levels using the numeric rating scale from baseline at 12 months in patients treated with adhesiolysis/neurolysis. (B) Change in functionality scores using the Oswestry Disability Index from baseline at 12 months in patients treated with adhesiolysis/neurolysis. CI: confidence interval, df: degrees of freedom.

neurolysis in managing lumbar disc herniation showed Level II or moderate evidence in the present systematic review and meta-analysis, which included one RCT and 5 observational studies with at least 6 months of follow-up in one study and 12 months of follow-up in all the others.

The single RCT by Gerdesmeyer et al. [25], in a well-designed, relevant, high-quality RCT, studied 90 patients with 44 patients in the placebo group and 46 patients in the neurolysis group. In the placebo design, a needle and catheter were inserted through a caudal approach. The needle was intentionally inserted without entering the spinal canal and the catheter was inserted into the subcutaneous tissue overlying the afflicted level. In the neurolysis group, the catheter was placed over the lumbar spine with adhesiolysis, followed by an injection of local anesthetic, hyaluronidase, and a steroid. In both groups, the catheters were left for 3 days and additional injections were performed.

The results showed, at one year, greater than 50% improvement in the ODI was seen in 90% of the patients in the lysis group, whereas it was seen in 35% of the patients in the placebo group. In reference to the observational studies, all 5 studies [31,33,37,38,40] were of moderate quality with inclusion of a large number of patients. Of the 5 studies meeting inclusion criteria, only one study by Park et al. [37] had less than 100 patients, with an inclusion of 78 patients. However, the other 4 studies included a large patient population ranging from 363 to 543 [31,33,38,40]. Total number of patients included in the observational studies were 1,821, assessing the role of percutaneous neurolysis in managing lumbar disc herniation or chronic lumbar radiculopathy. Consequently, the results of this study provide robust evidence from one high-quality RCT [25] and 5 observational studies [31,33,37,38,40] with a large proportion of patients with at least one-year follow-up in 4 studies [31,33,37,40] and 6-month follow-up in one study [38]. Overall, the number of patients included in long-term follow-up, including the RCT, were 1,268.

The present investigation is the first systematic review and meta-analysis focused on determining the role of neurolysis in managing chronic recalcitrant disc herniation or chronic lumbar radicular pain. The results of this systematic review and meta-analysis are similar to the results of systematic reviews and meta-analyses performed in post-lumbar surgery syndrome and central spinal stenosis [12-16]. Caudal epidural injections have been used since 1901, with a description of entering the epidural space from the sacral hiatus [1,42,43]. Epidural injections are also performed with an interlaminar or transforaminal approach [1]. However, the caudal approach, even though it requires

higher volumes, has been considered the safest and earliest technique. The most common approach for percutaneous neurolysis is through the sacral hiatus [1]. The majority of the studies were related to entry through the sacral hiatus. Administration of steroids in the epidural injections was described by Robecchi and Capra [44] and Lievre et al. [45] in 1952 and 1953. Effectiveness, safety, cost utility, and utilization patterns of epidural interventions have been extensively described [1,10,46-50].

Epidural injections have been shown to be with level I evidence in managing disc herniation or chronic lumbar radiculopathy with all 3 approaches, namely caudal, interlaminar, and transforaminal [1]. However, there also have been negative studies in the literature as well [51]. There have been significant discussions on this subject, including various types of bias in studies in interventional pain management [1,10]. In fact, Manchikanti et al. [10] performed a comparative systematic review and meta-analysis of the study by Chou et al. [51], which showed significantly different results when the analysis was performed utilizing methodology that did not convert active-controlled trials to placebo-controlled trials. Similar issues were also raised with findings of systematic reviews in assessing multiple interventional techniques, including the effectiveness of percutaneous adhesiolysis in post-lumbar surgery syndrome [13,15,16,52].

Limitations of this systematic review include lack of multiple RCTs, and the large scale observational studies are of only moderate quality.

In conclusion, the present systematic review and meta-analysis of epidural neurolysis in management of chronic recalcitrant disc herniation or lumbar radiculopathy shows level II evidence, based on one relevant, high-quality RCT [25] and 5 relevant moderate-quality observational studies [31,33,37,38,40]. The present analysis has not shown any significant side effects or complications derived from these studies.

ACKNOWLEDGMENTS

The authors wish to thank Bert Fellows, MA, Director Emeritus of Psychological Services at Pain Management Centers of America, for manuscript review, and Tonie M. Hatton and Diane E. Neihoff, transcriptionists, for their assistance in preparation of this manuscript.

CONFLICT OF INTEREST

Dr. Hirsch is a consultant for Medtronic and Senior Affiliate Research Fellow at the Neiman Policy Institute.

FUNDING

No funding to declare.

ORCID

Laxmaiah Manchikanti, https://orcid.org/0000-0002-4201-9063
Emilija Knezevic, https://orcid.org/0000-0002-7200-5295
Nebojsa Nick Knezevic, https://orcid.org/0000-0001-8028-1495
Mahendra R. Sanapati, https://orcid.org/0000-0002-1047-0765
Alan D. Kaye, https://orcid.org/0000-0003-2464-0187
Srinivasa Thota, https://orcid.org/0000-0002-3946-6751
Joshua A. Hirsch, https://orcid.org/0000-0002-9594-8798

REFERENCES

1. Manchikanti L, Knezevic NN, Navani A, Christo PJ, Limerick G, Calodney AK, et al. Epidural interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) comprehensive evidence-based guidelines. Pain Physician 2021; 24(S1): S27-208.
2. Mixter WJ, Barr JS. Rupture of the intervertebral disc with involvement of the spinal canal. N Engl J Med 1934; 211: 210-5.
3. Andersson G. Epidemiology of spinal disorders. In: The adult spine: principles and practice. 2nd ed. Edited by Frymoyer JW, Ducker TB, Hadler NM, Kostuik JP, Weinstein JN, Whitecloud TS 3rd. New York, Raven Press. 1997, pp 93-141.
4. Heliövaara M. Epidemiology of sciatica and herniated lumbar intervertebral disc. Helsinki, The Social Insurance Institution. 1988.
5. Friberg S, Hirsch C. Anatomical and clinical studies on lumbar disc degeneration. Acta Orthop Scand 1949; 19: 222-42.
6. Schultz A, Andersson G, Ortengren R, Haderspeck K, Nachemson A. Loads on the lumbar spine. Validation of a biomechanical analysis by measurements of intradiscal pressures and myoelectric signals. J Bone Joint Surg Am 1982; 64: 713-20.
7. Zhong M, Liu JT, Jiang H, Mo W, Yu PF, Li XC, et al. Incidence of spontaneous resorption of lumbar disc herniation: a meta-analysis. Pain Physician 2017; 20: E45-52.
8. Chiu CC, Chuang TY, Chang KH, Wu CH, Lin PW, Hsu WY. The probability of spontaneous regression of lumbar herniated disc: a systematic review. Clin Rehabil 2015; 29: 184-95.
9. Ahn SH, Ahn MW, Byun WM. Effect of the transligamentous extension of lumbar disc herniations on their regression and the clinical outcome of sciatica. Spine (Phila Pa 1976) 2000; 25: 475-80.
10. Manchikanti L, Knezevic NN, Boswell MV, Kaye AD, Hirsch JA. Epidural injections for lumbar radiculopathy and spinal

stenosis: a comparative systematic review and meta-analysis. Pain Physician 2016; 19: E365-410.
11. Oster BA, Kikanloo SR, Levine NL, Lian J, Cho W. Systematic review of outcomes following 10-year mark of Spine Patient Outcomes Research Trial for intervertebral disc herniation. Spine (Phila Pa 1976) 2020; 45: 825-31.
12. Helm S 2nd, Racz GB, Gerdesmeyer L, Justiz R, Hayek SM, Kaplan ED, et al. Percutaneous and endoscopic adhesiolysis in managing low back and lower extremity pain: a systematic review and meta-analysis. Pain Physician 2016; 19: E245-82.
13. Manchikanti L, Soin A, Boswell MV, Kaye AD, Sanapati M, Hirsch JA. Effectiveness of percutaneous adhesiolysis in post lumbar surgery syndrome: a systematic analysis of findings of systematic reviews. Pain Physician 2019; 22: 307-22.
14. Manchikanti L, Knezevic NN, Sanapati MR, Boswell MV, Kaye AD, Hirsch JA. Effectiveness of percutaneous adhesiolysis in managing chronic central lumbar spinal stenosis: a systematic review and meta-analysis. Pain Physician 2019; 22: E523-50.
15. Manchikanti L, Knezevic NN, Sanapati SP, Sanapati MR, Kaye AD, Hirsch JA. Is percutaneous adhesiolysis effective in managing chronic low back and lower extremity pain in post-surgery syndrome: a systematic review and meta-analysis. Curr Pain Headache Rep 2020; 24: 30.
16. Cho JH, Lee JH, Song KS, Hong JY, Joo YS, Lee DH, et al. Treatment outcomes for patients with failed back surgery. Pain Physician 2017; 20: E29-43.
17. Manchikanti L, Kosanovic R, Pampati V, Kaye AD. Declining utilization patterns of percutaneous adhesiolysis procedures in the fee-for-service (FFS) medicare population. Pain Physician 2021; 24: 17-29.
18. Heavner JE, Racz GB, Raj P. Percutaneous epidural neuroplasty: prospective evaluation of 0.9% NaCl versus 10% NaCl with or without hyaluronidase. Reg Anesth Pain Med 1999; 24: 202-7.
19. Racz GB, Racz GJ, Racz TA. Interventional pain management procedures. In: Pain management for clinicians: a guide to assessment and treatment. Edited by Noe C. Cham, Springer. 2020, pp 523-653.
20. McCarron RF. Epidural fibrosis: experimental model and therapeutic alternatives. In: Techniques of neurolysis. Edited by Racz GB. Boston, Kluwer Academic Publishers. 1989, pp 87-94.
21. Adams MA, Roughley PJ. What is intervertebral disc degeneration, and what causes it? Spine (Phila Pa 1976) 2006; 31: 2151-61.
22. Kuslich SD, Ulstrom CL, Michael CJ. The tissue origin of low back pain and sciatica: a report of pain response to tissue stimulation during operations on the lumbar spine using local anesthesia. Orthop Clin North Am 1991; 22: 181-7.
23. Zhu L, Huang Y, Hu Y, Tang Q, Zhong Y. Toll-like receptor 4/nuclear factor-kappa B pathway is involved in radicular pain by encouraging spinal microglia activation and inflammatory response in a rat model of lumbar disc herniation. Korean J Pain 2021; 34: 47-57.
24. Hazer DB, Acarbaş A, Rosberg HE. The outcome of epiduroscopy treatment in patients with chronic low back pain and radicular pain, operated or non-operated for lumbar disc herniation: a retrospective study in 88 patients. Korean J Pain 2018; 31: 109-15.
25. Gerdesmeyer L, Wagenpfeil S, Birkenmaier C, Veihelmann A, Hauschild M, Wagner K, et al. Percutaneous epidural lysis of adhesions in chronic lumbar radicular pain: a randomized, double-blind, placebo-controlled trial. Pain Physician 2013; 16: 185-96.
26. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [Internet]. PRISMA; 2021. Available at: http://prisma-statement.org/.
27. Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, et al.; Editorial Board of the Cochrane Back, Neck Group. 2015 updated method guideline for systematic reviews in the Cochrane Back and Neck Group. Spine (Phila Pa 1976) 2015; 40: 1660-73.
28. Manchikanti L, Hirsch JA, Cohen SP, Heavner JE, Falco FJ, Diwan S, et al. Assessment of methodologic quality of randomized trials of interventional techniques: development of an interventional pain management specific instrument. Pain Physician 2014; 17: E263-90.
29. Manchikanti L, Hirsch JA, Heavner JE, Cohen SP, Benyamin RM, Sehgal N, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of nonrandomized studies of interventional techniques. Pain Physician 2014; 17: E291-317.
30. Manchikanti L, Falco FJ, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. Pain Physician 2014; 17: E319-25.
31. Cho PG, Ji GY, Yoon YS, Shin DA. Clinical effectiveness of percutaneous epidural neuroplasty according to the type of single-level lumbar disc herniation: a 12-month follow-up study. J Korean Neurosurg Soc 2019; 62: 681-90.
32. Moon SH, Park JY, Cho SS, Cho HS, Lee JY, Kim YJ, et al. Comparative effectiveness of percutaneous epidural adhesiolysis for different sacrum types in patients with chronic pain due to lumbar disc herniation: a propensity score matching analysis. Medicine (Baltimore) 2016; 95: e4647.
33. Moon SH, Lee JI, Cho HS, Shin JW, Koh WU. Factors for predicting favorable outcome of percutaneous epidural adhesiolysis for lumbar disc herniation. Pain Res Manag 2017; 2017: 1494538.
34. Taheri A, Khajenasiri AR, Nazemian Yazdi NA, Safari S, Sadeghi J, Hatami M. Clinical evaluation of percutaneous caudal epidural adhesiolysis with the Racz technique for low back pain due to contained disc herniation. Anesth Pain Med 2016; 6: e26749.

35. Cho S, Park HS. Percutaneous epidural adhesiolysis with epidural steroid injection: a non-inferiority test of non-particulate steroids versus particulate steroids. Pain Med 2016; 17: 1612-9.
36. Kalagac Fabris L, Šuput A, Gusić N, Mamontov P. Epidural adhesiolysis in the management of chronic low back pain in failed back surgery syndrome and in lumbar radicular pain: first year of experience at Pula General Hospital, Pula, Croatia – a randomized trial. Acta Med Croatica 2019; 73: 57-65.
37. Park SH, Ji GY, Cho PG, Shin DA, Yoon YS, Kim KN, et al. Clinical significance of epidurography contrast patterns after adhesiolysis during lumbar percutaneous epidural neuroplasty. Pain Res Manag 2018; 2018: 6268045.
38. Choi EJ, Yoo YJ, Lee PB, Kim YC, Lee SC, Moon JY. A retrospective study to evaluate the effect of concentration of hypertonic saline on efficacy and safety of epidural adhesiolysis. Anesth Analg 2017; 124: 2021-9.
39. Lee JH, Lee SH. Clinical effectiveness of percutaneous adhesiolysis using Navicath for the management of chronic pain due to lumbosacral disc herniation. Pain Physician 2012; 15: 213-21.
40. Ji GY, Oh CH, Moon B, Choi SH, Shin DA, Yoon YS, et al. Efficacy of percutaneous epidural neuroplasty does not correlate with dural sac cross-sectional area in single level disc disease. Yonsei Med J 2015; 56: 691-7.
41. Veihelmann A, Devens C, Trouillier H, Birkenmaier C, Gerdesmeyer L, Refior HJ. Epidural neuroplasty versus physiotherapy to relieve pain in patients with sciatica: a prospective randomized blinded clinical trial. J Orthop Sci 2006; 11: 365-9.
42. Sicard MA. [Extradural drug injections by saracoccygiane route]. C R Seances Soc Biol Fil 1901; 53: 396-8. French.
43. Ter Meulen BC, Weinstein H, Ostelo R, Koehler PJ. The epidural treatment of sciatica: its origin and evolution. Eur Neurol 2016; 75: 58-64.
44. Robecchi A, Capra R. [Hydrocortisone (compound F); first clinical experiments in the field of rheumatology]. Minerva Med 1952; 43: 1259-63. Italian.
45. Lievre JA, Bloch-Mechel H, Pean G, Uro J. [Hydrocortisone in local injection]. Rev Rhum Mal Osteoartic 1953; 20: 310-1. French.
46. Manchikanti L, Sanapati MR, Pampati V, Boswell MV, Kaye AD, Hirsch JA. Update on reversal and decline of growth of utilization of interventional techniques in managing chronic pain in the Medicare population from 2000 to 2018. Pain Physician 2019; 22: 521-36.
47. Manchikanti L, Soin A, Mann DP, Bakshi S, Pampati V, Kaye AD, et al. Utilization patterns of facet joint interventions in managing spinal pain: a retrospective cohort study in the US fee-for-service Medicare population. Curr Pain Headache Rep 2019; 23: 73.
48. Manchikanti L, Pampati V, Soin A, Sanapati MR, Kaye AD, Hirsch JA. Declining utilization and inflation-adjusted expenditures for epidural procedures in chronic spinal pain in the Medicare population. Pain Physician 2021; 24: 1-15.
49. Manchikanti L, Pampati V, Parr Iii A, Manchikanti MV, Sanapati MR, Kaye AD, et al. Cervical interlaminar epidural injections in the treatment of cervical disc herniation, post surgery syndrome, or discogenic pain: cost utility analysis from randomized trials. Pain Physician 2019; 22: 421-31.
50. Manchikanti L, Pampati V, Benyamin RM, Hirsch JA. Cost utility analysis of lumbar interlaminar epidural injections in the treatment of lumbar disc herniation, central spinal stenosis, and axial or discogenic low back pain. Pain Physician 2017; 20: 219-28.
51. Chou R, Hashimoto R, Friedly J, Fu R, Bougatsos C, Dana T, et al. Epidural corticosteroid injections for radiculopathy and spinal stenosis: a systematic review and meta-analysis. Ann Intern Med 2015; 163: 373-81.
52. Manchikanti L, Kaye AD, Soin A, Albers SL, Beall D, Latchaw R, et al. Comprehensive evidence-based guidelines for facet joint interventions in the management of chronic spinal pain: American Society of Interventional Pain Physicians (ASIPP) guidelines facet joint interventions 2020 guidelines. Pain Physician 2020; 23(3S): S1-127.