Systematic Review

Effectiveness of Percutaneous Adhesiolysis in Managing Chronic Central Lumbar Spinal Stenosis: A Systematic Review and Meta-Analysis

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Background: Symptomatic lumbar spinal stenosis is a condition affecting a growing number of individuals resulting in significant disability and pain, leading to a multitude of interventions ranging from simple over the counter medication to opioids, and, finally, to complex surgical fusions. After failure of conservative treatment with drug therapy, physical therapy, and other conservative modalities including epidural injections, percutaneous adhesiolysis with targeted delivery of drugs into the epidural space can be offered in lumbar central spinal stenosis prior to minimally invasive surgical options or complex surgical fusions. To date there has been only one systematic review which has assessed the role of percutaneous adhesiolysis in treating central spinal stenosis, compared to post lumbar surgery syndrome which has multiple systematic reviews and randomized controlled trials (RCTs).

Study Design: A systematic review of RCTs and observational studies assessing the role of percutaneous adhesiolysis in managing lumbar central spinal stenosis.

Objective: To evaluate the effectiveness of percutaneous adhesiolysis in managing central lumbar spinal stenosis, utilizing currently available literature.

Methods: This systematic review was performed utilizing Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for literature search, Cochrane review criteria, Interventional Pain Management techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB), and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM-QRBNR) to assess methodologic quality assessment and qualitative analysis utilizing best evidence synthesis principles, and meta-analysis.

PubMed, Cochrane library, US National Guideline Clearinghouse, Google Scholar, and prior systematic reviews and reference lists were utilized in the literature search from 1966 through June 2019. The evidence was summarized utilizing principles of the best evidence synthesis on a scale of 1 to 5.

Outcome Measures: The primary outcome or hard endpoint was defined as the proportion of patients with 50% pain relief and improvement in functionality, whereas the secondary outcome measures or soft endpoints were pain relief and/or improvement in functionality. Short-term effectiveness was defined as improvement of 6 months or less, whereas long-term effectiveness was defined as more than 6 months.

Results: Based on search criteria, 9 manuscripts were identified and considered for inclusion with final inclusion of 2 RCTs and 4 observational studies in this systematic review and 5 studies for single arm meta-analysis. The results showed Level II evidence for short-term and long-term improvement in pain and function with application of percutaneous adhesiolysis in managing central lumbar spinal stenosis.

Limitations: There was a significant paucity of evidence assessing the role of percutaneous adhesiolysis in managing lumbar central spinal stenosis, leading to Level II or strong evidence.

Conclusion: Overall, the present analysis shows Level II (moderate) evidence for percutaneous adhesiolysis in managing lumbar central spinal stenosis based on relevant high quality RCTs and observational studies.

Key Words: Lumbar central spinal stenosis, percutaneous adhesiolysis, randomized controlled trials, systematic reviews, neuroplasty

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Lumbar central spinal stenosis is a narrowing of the spinal canal producing radiculopathy or neurogenic claudication, first defined by Verbiest (1). Spinal stenosis has been shown to be present in over 27% of the population (2). Spinal stenosis is the most common reason for lumbar spine surgery in persons older than 65 years of age in the United States (3-10). Major symptoms of central spinal stenosis including neurogenic claudication or radicular pain may be related to a neurovascular mechanism such as reduced arterial flow in the cauda equina, venous congestion, and increased epidural pressure (11-15). Related to the complex nature of central spinal stenosis, it has been described as a multifactorial disorder with clinical presentation which can be variable with or without neurogenic claudication manifested by pain in the buttocks or legs when walking, which disappears with sitting or lumbar flexion (11,16). However, spinal stenosis may also be asymptomatic in many patients despite radiological diagnosis evidence (17,18). Spinal stenosis has been commonly managed by various modalities of treatments including over-the-counter medication, interventional techniques, minimally invasive and complex surgical fusions (3-11,19-54). Among interventional modalities, epidural injections have commonly been utilized and their effectiveness has been demonstrated in randomized controlled trials (RCTs) (20,21) and systematic reviews (19,30). Their cost utility analysis was demonstrated (33,34). Further, in patients with inadequate relief, percutaneous adhesiolysis has been utilized (35-37).

The use of percutaneous adhesiolysis to manage lumbar spinal stenosis was first described in 2001 in an observational report (55). Subsequently, the first RCT assessing the effectiveness of percutaneous adhesiolysis in lumbar central spinal canal stenosis was published by Manchikanti et al (35) in 2013 in a prospective evaluation with a 2-year follow-up. The initial study (56) was double-blind, randomized, with a comparison of percutaneous adhesiolysis with caudal epidural injections; however, 25 patients from the adhesiolysis group were continued with follow-up, along with 45 additional patients, leading to a total of 70 patients in the adhesiolysis group for the 2-year follow-up. The overall results showed a primary outcome or significant pain relief and functional status improvement of 50% or more in 71% of patients at the end of 2 years. The overall number of procedures over a period of 2 years was 5.7 ± 2.73. Since then, multiple other studies have been published showing the effectiveness of percutaneous adhesiolysis in managing spinal stenosis (57-60). Manchikanti et al (35,75) included only patients who failed to respond to epidural injections. A systematic review of percutaneous adhesiolysis, which included all groups of patients including spinal stenosis and post lumbar surgery syndrome, showed Level II evidence in managing spinal stenosis with adhesiolysis (36). Manchikanti et al (61) performed a systematic review of systematic reviews analyzing various deficiencies in the systematic reviews and high-quality systematic reviews and high-quality randomized trials were assessed without bias. There was significant evidence of effectiveness of percutaneous adhesiolysis in post lumbar surgery syndrome; however, at present, no such data is available for central spinal stenosis.

With continued controversy in managing central spinal stenosis with various modalities of surgical interventions and interventional techniques, it is unclear which modality is most effective; although, interventional techniques have been shown to be clinically effective and cost-effective in spinal stenosis and other conditions (19-22,30,33-37,57-65). Overall, cost utility analysis has previously demonstrated percutaneous adhesiolysis to be effective at a cost of $4,426 (37) or improvement of one year of quality-adjusted life year (QALY). These costs were similar to lumbar interlaminar epidural injections of $3,301 (34), caudal epidural injections of $3,628 (33), therapeutic lumbar facet joint nerve blocks of $4,432 (62), cervical therapeutic facet joint nerve blocks of

$4,261 (63), thoracic epidural injections of $3,245.12 (64), and cervical epidural injections of $3,786 per QALY (65). Thus, these costs are far less than surgical interventions of $69,403 for disc herniation (66) and $77,600 in managing spinal stenosis with degenerative spondylolisthesis, and $115,600 in managing spinal stenosis with degenerative spondylolisthesis (10), and even spinal cord stimulation of €5,624 (about $8,400 in 2010) for QALY (67).

Consequently, this systematic review and meta-analysis was undertaken to assess the effective of percutaneous adhesiolysis in managing chronic low back and lower extremity pain secondary to lumbar central spinal canal stenosis.

Methods

The present systematic review was performed based on methodological and reporting quality of systematic reviews as described by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (68).

This systematic review and meta-analysis focus on the effectiveness of percutaneous adhesiolysis in managing chronic low back pain and lower extremity pain secondary to lumbar central spinal canal stenosis.

Eligibility Criteria

Types of Studies

Randomized controlled trials
Observational studies

Types of Participants

All participants with chronic low back and lower extremity pain secondary to lumbar central spinal canal stenosis treated with percutaneous adhesiolysis with or without a control group.

Types of Interventions

Percutaneous adhesiolysis administered utilizing caudal, lumbar interlaminar, or lumbar transforaminal approaches, RCTs with control group or active control studies, studies utilizing one day or 3-day procedures, and studies utilizing various types of injectates.

Types of Outcome Measures

- The primary outcome or hard endpoint was proportion of patients with 50% pain relief and improvement in functionality, whereas secondary outcome measures, or soft endpoints, were pain relief and/or improvement in functionality.

Data Sources

All available trials in the English language, or with available translation, from all countries, providing appropriate management with outcome evaluations of at least 3 months were considered for inclusion. Searches were performed from PubMed from 1966 www.ncbi.nlm.nih.gov/pubmed, Cochrane Library www.thecochranelibrary.com, US National Guideline Clearinghouse (NGC) www.guideline.gov/, clinical trials www.clinicaltrials.gov/, and Google Scholar with search period through June 2019.

Search Strategy

The search strategy emphasized chronic low back pain with lumbar spinal stenosis treated with percutaneous adhesiolysis.

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 spinal stenosis) AND ((((((((((epidural injection) OR epidural adhesiolysis) OR epidural neuroplasty) OR epidural lysis of adhesions) OR percutaneous adhesiolysis 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])))).

Data Collection and Analysis

This review focused on all types of evaluations of evaluations of assessment of effectiveness of lumbosacral central spinal stenosis. All studies that provided appropriate management and included outcome evaluations and statistical evaluations were reviewed. Book chapters, case reports, and reports without an appropriate diagnosis were excluded from consideration.

Inclusion Criteria

This review focused only on studies of effectiveness. The population of interest was patients suffering from neurogenic claudication or lumbar radicular pain with or without low back pain secondary to lumbar

central spinal stenosis. Patients with acute trauma, fractures, malignancies, and inflammatory diseases were excluded.

All randomized trials with appropriate statistical calculations were utilized. Observational studies with a sample size of at least ten subjects were included.

Duplicate studies were also eliminated as the data included was from the same patients in both studies.

Data Collection Process

A standardized search criteria was utilized for relevant literature in an unblinded manner with 2 review authors. These review authors selected the manuscripts and extracted the data from the included studies. If there was a disagreement among the reviewers, the third author was involved. All conflicts of interest were eliminated by eliminating the authors of any of the manuscripts to review them.

Data Synthesis and Analysis

The quality assessment of each individual manuscript was also carried out by 2 authors. Analysis of the evidence was performed by 2 authors independently. Evidence synthesis was performed by 3 authors including the statistician. All conflicts were resolved as stated above.

Risk of Bias of Individual Studies

The quality of each individual article used in this analysis was assessed using the Cochrane Review rating system (Appendix Table 1) (69) and Interventional Pain Management Techniques -- Quality Appraisal of Reliability and Risk of Bias Assessment Tool (IPM – QRB) for randomized controlled trials (Appendix Table 2) (70), and Interventional Pain Management Techniques – Quality Appraisal of Reliability and Risk of Bias Assessment for nonrandomized or observational studies (IPM-QRBNR) (Appendix Table 3) (71).

Utilizing the Cochrane Review criteria, studies meeting at least 9 of the 13 inclusion criteria were considered high-quality. Those 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, studies meeting the inclusion criteria but scoring less than 16 were considered low quality and were excluded, studies scoring from 16 to 31 were considered moderate quality; and studies scoring from 32 to 48 were considered high quality and were included.

Methodologic quality assessment of each manuscript was performed by 2 review authors. The assessment was carried out independently in an unblinded, standardized manner to assess the methodologic quality and internal validity of all the studies considered for inclusion. If discrepancies occurred, a third reviewer performed an assessment, and a consensus was reached. Further remaining issues were discussed by all reviewers and were then resolved.

Outcome of the Studies

For the present analysis, either 50% relief from the baseline pain score or a change of at least 3 points on an 11-point pain scale of 0 to 10 was considered clinically significant. For functional status improvement, a change of 30% or more on disability scores or 50% improvement from baseline was considered clinically significant.

A study was judged to be positive if the relevance and effectiveness of the regenerative injection therapy of interest was demonstrated with either a control group or upon comparison from baseline to follow-up. A negative study was defined as one where no difference was seen between the treatments or where no improvement from baseline could be measured. Reference point measurements were considered at 3 months, 6 months, and one year.

Analysis of Evidence

The analysis of the evidence was performed based on best-evidence synthesis and was modified and collated using multiple available criteria, including the Cochrane Review criteria and United States Preventive Services Task Force (USPSTF) criteria as illustrated in Table 1 (72). The analysis was conducted using 5 levels of evidence ranging from strong to opinion- or consensus-based. The results of best evidence as per grading were utilized. At least 2 of the review authors independently, in an unblinded, standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus was attained. If there were any conflicts of interest (e.g., authorship), the reviewers of interest were recused from assessment and analysis.

Meta-analysis

For conventional or dual-arm meta-analysis software Review Manager (Rev Man 5.3) was used (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark, 2008).

Table 1. *Qualitative modified approach to grading of evidence.*

Level I	Strong	Evidence obtained from multiple relevant high quality randomized controlled trials
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
Level III	Fair	Evidence obtained from at least one relevant moderate or low quality randomized controlled trial with multiple relevant observational studies or Evidence obtained from at least one relevant high quality nonrandomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Limited	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Consensus based	Opinion or consensus of large group of clinicians and/or scientists

Adapted from Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (72).

For single-arm meta-analysis software Comprehensive Meta-analysis version 3.0 was used (Biostat Inc., Englewood, NJ).

For pain and improvement of function data, the studies were reported as the standardized mean differences (SMD) with 95% confidence intervals (CI).

Data were plotted by using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I2 statistics.

For pain and functionality improvement data, the studies were reported as the Mean differences (MD) with 95% CI.

Data were plotted using forest plots to evaluate treatment effects. Heterogeneity was interpreted through I^2 statistics.

All analyses were based on each modality of treatment and the solution injected. Short-term improvement was defined as any improvement of 3 months and long-term evidence was described as greater than 6 months.

Results

Study Selection

Figure 1 shows a flow diagram of the study selection using the PRISMA study selection process (68).

Based on the search criteria, 9 manuscripts were identified and considered for inclusion (35,55-60,73,74).

Three studies (55,74,75) were excluded. Finally, 2 RCTs (56,56) and 4 observational studies (35,58,60,73) were included in the systematic review and meta-analysis.

Methodologic Quality and Risk of Bias Assessment

Of the 6 manuscripts meeting inclusion criteria (35,56-58,60,73), 2 were randomized trials (56,57). Tables 2 and 3 show the methodologic quality assessment and risk of bias in each of these trials utilizing the Cochrane review criteria and the IPM-QRB criteria respectively (69,70). Assessment by the Cochrane review criteria and IPM-QRB showed both trials to be of high quality (56,57).

Table 4 shows the assessment of the included nonrandomized or observational studies, including case reports, utilizing IPM-QRBNR criteria. Four studies (35,58,60,71) were included. Assessment by IPM-QRBNR showed one study to be of high quality (35), with the remaining 3 studies of moderate quality (58,60,73).

Study Characteristics

Table 5 shows the characteristics and outcomes of the studies meeting inclusion criteria with receiving percutaneous adhesiolysis for central lumbar spinal stenosis.

These studies were heterogeneous. There were only 2 RCTs. One RCT (56) was high quality with appropriate design and follow-up of one-year with 25 patients in the percutaneous adhesiolysis group and 25 patients in the caudal epidural injection group with catheter being placed at S1. This study showed positive results at 3, 6, and 12 months in a significant proportion of patients, with the defined parameter of significant improvement considered as significant pain relief and functional status improvement of 50%. The second RCT (57) compared, in an active control design, percutaneous adhesiolysis with use of Racz catheter (considered as balloonless catheter) and an inflatable balloon catheter utilizing Zineu catheter. In the Zineu catheter group, after appropriate adhesiolysis at multiple levels and administration of some drugs, a Perifix catheter was placed which was left for 2 days. Patients also re-

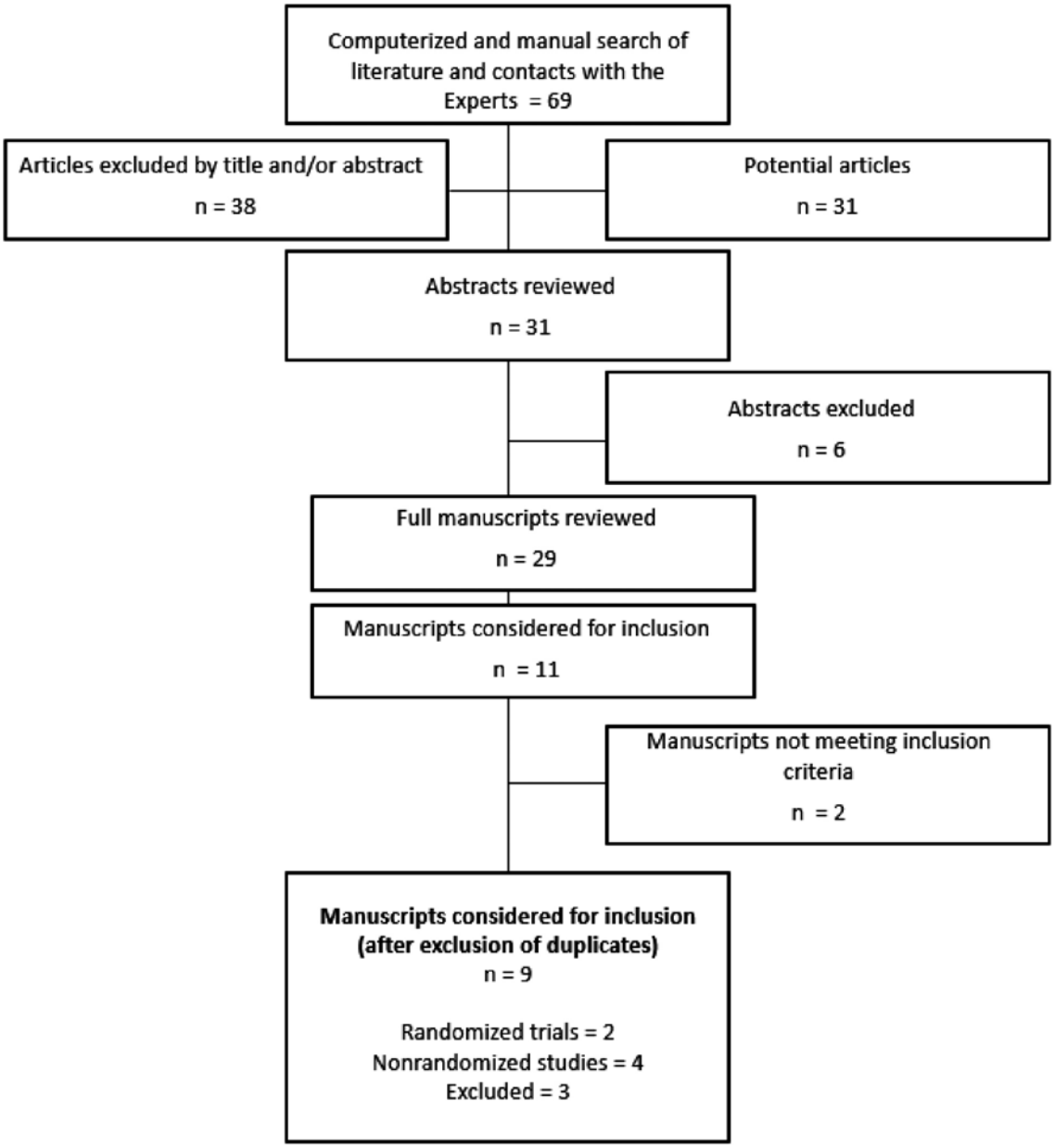


Fig. 1. *Flow diagram illustrating published literature evaluating the effectiveness of percutaneous adhesiolysis in managing central spinal canal stenosis.*

ceived a second day administration of the drugs in both groups. Even though based on the available findings, it appears that this was a high-quality study, there may be significant differences in outcomes assessment and blinding. Further, of the 30 patients in each group allocated for treatment, 20 patients in the adhesiolysis group, and 24 patients in the implantable balloon catheter group were included.

The remaining 4 studies were of a retrospective nature. One of the studies was related to inflatable balloon catheter (58), which is a predecessor to the RCT (57). However, the results were negative in the initial

Table 2. *Methodological quality assessment of randomized trials utilizing Cochrane review criteria.*

	Manchikanti et al (56)	Karm et al (57)
Randomization adequate	+	+
Concealed treatment allocation	+	+
Patient blinded	+	+
Care provider blinded	--	--
Outcome assessor blinded	--	--
Drop-out rate described	+	+
All randomized participants analyzed in the group	+	+
Reports of the study free of suggestion of selective outcome reporting	+	+
Groups similar at baseline regarding most important prognostic indicators	+	+
Co-interventions avoided or similar	+	+
Compliance acceptable in all group	+	+
Time of outcome assessment in all groups similar	+	+
Are other sources of potential bias not likely	+	+
Score	11/13	11/13

Y = Yes; N = No; U = Unclear
Source: Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW; 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; 40:1660-1673 (69).

study with the balloon inflatable catheter. Thus, it raises questions in reference to advantages of inflatable catheters. The second observational study was an extension of the RCT (35). This study showed good results in 70 patients followed for 24 months. Overall, the primary outcome of significant pain relief and functional status improvement of 50% or more was seen in 71% of the patients at the end of the 2 years. The overall number of procedures over a period of 2 years was 5.7 ± 2.73. Among the remaining 2 studies, one study assessed clinical effectiveness of percutaneous adhesiolysis and predictive factors of treatment efficacy in patients with lumbosacral stenosis. This study showed moderate results with successful outcomes at 3 months with a single treatment in 48% of the patients. This study was not well designed as they included a significant proportion of patients with spondylolisthesis, post lumbar surgery syndrome and severe spinal stenosis at various levels.

Table 3. *Methodologic quality assessment of randomized trials utilizing IPM – QRB.*

		Manchikanti et al (56)	Karm et al (57)
I.	TRIAL DESIGN AND GUIDANCE REPORTING		
1.	CONSORT or SPIRIT	2	2
II.	DESIGN FACTORS		
2.	Type and Design of Trial	2	2
3.	Setting/Physician	2	2
4.	Imaging	3	3
5.	Sample Size	2	1
6.	Statistical Methodology	1	1
III.	PATIENT FACTORS		
7.	Inclusiveness of Population	2	2
8.	Duration of Pain	2	2
9.	Previous Treatments	2	2
10.	Duration of Follow-up with Appropriate Interventions	2	2
IV.	OUTCOMES		
11.	Outcomes Assessment Criteria for Significant Improvement	4	2
12.	Analysis of all Randomized Participants in the Groups	1	1
13.	Description of Drop Out Rate	1	1
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	1	1
15.	Role of Co-Interventions	1	1
V.	RANDOMIZATION		
16.	Method of Randomization	2	2
VI.	ALLOCATION CONCEALMENT		
17.	Concealed Treatment Allocation	1	2
VII.	BLINDING		
18.	Patient Blinding	1	1
19.	Care Provider Blinding	0	0
20.	Outcome Assessor Blinding	0	0
VIII.	CONFLICTS OF INTEREST		
21.	Funding and Sponsorship	2	2
22.	Conflicts of Interest	2	2
TOTAL		36	34

Source: Manchikanti L, 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-E290 (70).

Table 4. *IPM checklist for assessment of nonrandomized or observational studies meeting inclusion criteria utilizing IPM - QRBNR.*

		Manchikanti et al (35)	Choi et al (58)	Lee & lee (60)	Choi et al (73)
I.	STUDY DESIGN AND GUIDANCE REPORTING				
1.	STROBE or TREND GUIDANCE	2	2	2	2
II.	DESIGN FACTORS				
2.	Study Design and Type	3	3	2	2
3.	Setting/Physician	2	2	2	2
4.	Imaging	3	3	3	3
5.	Sample Size	0	0	1	0
6.	Statistical Methodology	2	2	2	2
III.	PATIENT FACTORS				
7.	Inclusiveness of Population	4	2	0	0
8.	Duration of Pain	2	2	2	2
9.	Previous Treatments	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	4	2	1	1
IV.	OUTCOMES				
11.	Outcomes Assessment Criteria for Significant Improvement	4	2	2	2
12.	Description of Drop Out Rate	2	0	2	1
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	0	0	0
14.	Role of Co-Interventions	2	2	2	2
V.	ASSIGNMENT				
15.	Method of Assignment of Participants	2	2	0	0
VI.	CONFLICTS OF INTEREST				
16.	Funding and Sponsorship	2	2	2	2
TOTAL		36	28	25	24

Source: Manchikanti L, et al. Development of an interventional pain management specific instrument for methodologic quality assessment of non-randomized studies of interventional techniques. *Pain Physician* 2014; 17:E291-E317 (71).

The results were appropriate in patients without associated comorbidities of post-surgery syndrome, severe stenosis, or spondylolisthesis. Obviously, adhesiolysis is more effective in patients with central spinal stenosis, which is moderate; however, this study also demonstrates that it is also effective in patients with spondylolisthesis and severe stenosis even though to a lesser extent. Another study (59) evaluated prognostic predictors of percutaneous adhesiolysis using a Racz catheter in patients with post lumbar surgery syndrome or spinal stenosis. They included 35% of patients with previous lumbar surgery and 33% of the patients with foraminal stenosis. Consequently, results were borderline.

Qualitative Analysis

Qualitative analysis was performed utilizing a modified approach of grading of evidence (72) with moderate (Level II) evidence from one relevant high-quality RCT and multiple relevant high-quality and moderate-quality observational studies. Majority of the studies consistently showed the improvement in patients undergoing adhesiolysis, however one RCT showed better evidence for the inflatable catheter (57). These results were not replicated in other studies. Overall, with percutaneous adhesiolysis, outcomes showed improvement in as high as 71% of the patients at the end of a 2-year follow-up.

Quantitative Analysis

Single-arm Meta-analysis

Table 5. *Characteristics of included studies of percutaneous adhesiolysis in lumbar central canal stenosis.*

Study Study Characteristics Methodological Quality Scoring	**Participants and Interventions**	**Outcome Measures**	**Pain Relief and Function**			**Results**			**Comment(s)**
			3 mos.	**6 mos.**	**12 mos.**	**Short-term ≤ 3 mos.**	**Long-Term**		
							> 6 mos.	**≥ 12 mos.**	
Manchikanti et al (56) Randomized controlled trial Quality Scores: Cochrane = 11/13 IPM-QRB = 36/48	50 patients Percutaneous adhesiolysis = 25 patients Caudal epidural injections = 25 patients Intervention: Adhesiolysis with Racz catheter, followed by injection of 5 mL of 2% preservative free lidocaine and subsequent injection of 6 mL of 10% hypertonic sodium chloride solution and 6 mg of nonparticulate betamethasone Control group: Catheter passed to S2 with injection of 5 mL of 2% preservative free lidocaine with subsequent injection of 6 mL of 0.9% sodium chloride solution and 6 mg of nonparticulate betamethasone There was reduction of opioid intake in the assessment.	NRS, ODI, employment status, opioid intake, Significant improvement = 50% or more pain relief and improvement in functional status	28% vs 80%	12% vs 80%	4% vs 76%	P	P	P	•This is the first RCT conducted in managing chronic low back pain secondary to lumbar central spinal canal stenosis with percutaneous adhesiolysis. •The treatment was offered based on return of pain. •Robust outcome criteria were utilized. •High quality study with positive results
Karm et al (57) Randomized controlled trial Quality Scores: Cochrane = 11/13 IPM-QRB = 34/48	44 patients Adhesiolysis with Racz or NaviCath catheter = 20 patients Adhesiolysis with inflatable balloon catheter = 24 patients Adhesiolysis with catheter without balloon received adhesiolysis, injections of 2 mL of 1% lidocaine with steroid, 5 mg of dexamethasone, and 15 IU hyaluronidase. In the recovery room patients received 2 mL of lidocaine, 10 mL of 10% hypertonic saline for 2 days Inflatable balloon catheter adhesiolysis followed by injection of 4 mL of 1% lidocaine, and 15 IU of hyaluronidase. After adhesiolysis 5 mg of dexamethasone and 1% lidocaine at each target site, 2 mL each was injected. In the recovery room a test injection of 2 mL of 1% lidocaine and additional 4 mL of 10% hypertonic saline through the Perifix catheter for 2 days.	NRS, ODI, Global Perceived Effect of Satisfaction, Medication Quantification Scale III	40% adhesiolysis group 58% in inflatable balloon catheter group	25% adhesiolysis group 58% in inflatable balloon catheter group	NA	N	N = adhesiolysis P = inflatable catheter	NA	•In a complicated assessment, authors compared an inflatable balloon catheter and a balloonless catheter in central lumbar spinal stenosis. •Authors performed a 2-day procedure in both groups. Inflatable balloon catheter showed significantly better improvement with 58% of the patients considered as successful responders and 40% at 3 months and 25% at 6 months in balloonless catheter group. •Overall this is considered as a negative study for adhesiolysis with Racz catheter, whereas it was considered as positive for inflatable balloon catheter.

Table 5 (cont.). *Characteristics of included studies of percutaneous adhesiolysis in lumbar central canal stenosis.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
			3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	Long-Term		
							> 6 mos.	≥ 12 mos.	
Choi et al (58) Single arm, prospective observational study Quality Scores: IPM-QRB = 28/48	61patients Adhesiolysis with a single combined treatment with balloon inflatable catheter Zineu. Intervention included adhesiolysis with an inflatable balloon catheter Zineu, with injection of 4 mL of 1% lidocaine and 1,500 IU of hyaluronidase. Balloon adhesiolysis was followed by placement of the catheter and injection of 2 mL of 1% lidocaine with steroid, 5 mg of dexamethasone or 20 mg of triamcinolone at each target site. Second day, 10% hypertonic saline and steroids were injected.	NRS, ODI measures at 1, 3, 6, and 12 months, 50% or more than 4 point reduction in NRS	38%	39%	31%	Limited	N = due to significant loss of follow-up with highest improvement reaching 39% with 50% reduction in NRS However, authors have described successful responders at 61% at 3 months, 57% at 6 months, and 36% at 12 months with a single procedure utilizing greater than 30% or improvement in 2 point reduction in NRS which is a very low target.	NA	•Patients with severe stenosis and also significant proportion of patients with foraminal stenosis, 31%, were included. •There was large number of patients missing follow-up at end of one-year.

Table 5 (cont.). *Characteristics of included studies of percutaneous adhesiolysis in lumbar central canal stenosis.*

Study Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
			3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	Long-Term		
							> 6 mos.	≥ 12 mos.	
Manchikanti et al (35) Prospective evaluation Quality Scores: IPM-QRBNR = 36/48	• Continuation of a randomized, double blind intervention group of percutaneous adhesiolysis of 25 patients with addition of 45 patients with a total of 70 patients. • All patients received percutaneous adhesiolysis and appropriate placement of Racz catheter. • Injection included 5 mL of 2% preservative free lidocaine and 6 mL of 10% hypertonic sodium chloride solution and 6 mg of nonparticulate betamethasone. • Average number of procedures for one year = 3.3 ± 1.07 • Average number of procedures for 2 years = 5.7 ± 2.73	NRS, ODI, employment status, opioid intake, Significant improvement = 50% or more pain relief and improvement in functional status	78%	71%	61%	P	P	P	•Large scale study with 70 patients with robust outcomes measures showing positive results with repeat procedures of percutaneous adhesiolysis.
Lee & Lee (60) Retrospective study Quality Scores: IPM-QRBNR = 25/48	65 patients Adhesiolysis was performed with NaviCath followed by injection of 3 mL of contrast, followed by injection 4 mL of 1% lidocaine and 40 mg of triamcinolone. No hypertonic saline or hyaluronidase was injected.	NRS, ODI Successful pain relief and functional improvement were described as 50% and 40% or more reduction in NRS and ODI	The relief was seen in 54% of the patients for back pain, 51% for leg pain, and 48% with functional status improvement.	NA	NA	P	NA	NA	•A retrospective study with limited number of patients attempting to study multiple variables. •Overall results were positive or borderline positive. •Authors showed that spondylolisthesis, previous lumbar surgery, and foraminal stenosis were associated with significant higher proportion of unsuccessful results in patients without previous surgery. •17 of 30 patients or 57% showed successful result without comorbidity of surgery. Similarly patients without spondylolisthesis showed a success rate of 18 of 30 patients or 60%.

Table 5 (cont.). *Characteristics of included studies of percutaneous adhesiolysis in lumbar central canal stenosis.*

Study Characteristics Methodological Quality Scoring	Participants and Interventions	Outcome Measures	Pain Relief and Function			Results			Comment(s)
			3 mos.	6 mos.	12 mos.	Short-term ≤ 3 mos.	Long-Term		
							> 6 mos.	≥ 12 mos.	
Choi et al (73) Retrospective assessment Quality Scores: IPM-QRB = 24/48	78 patients studied with percutaneous adhesiolysis with caudal approach. Following appropriate adhesiolysis, 5 mL of 0.25% ropivacaine containing 1,500 units or hyaluronidase was injected in the recovery room. 6 mL of 10% sodium chloride solution was injected. Following this, 2 mL of 0.9% sodium chloride solution containing 40 mg of triamcinolone was injected.	Pain relief. Assessment of proportion of patients based on severity of the stenosis.	51.1% successful response	49% successful response	NA	P	P	NA	•Small retrospective assessment in 78 patients with positive results with a single treatment in 51% of the patients at 3 months and 49% of the patients at 6 months. •Authors also included a large number of patients with previous surgery of 37% of the patients. They also included 33% with foraminal stenosis. In addition severe stenosis was seen in 13% of the patients and root compression in 46% of the patients providing somewhat mixed results.

RCT = randomized controlled trial; NRS = Numeric Pain Rating Scale; ODI = Oswestry Disability Index; 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 Nonrandomized Studies; NA =Not Applicable; N = negative; P = positive

Conventional-arm analysis was not feasible due to heterogeneity among the only 2 RCTs available. Consequently, single-arm meta-analysis was performed. Single-arm meta-analysis was performed for percutaneous adhesiolysis for pain relief and functional status improvement utilizing data from 5 studies (35,56-58,60).

Pain and Functionality at 3 months

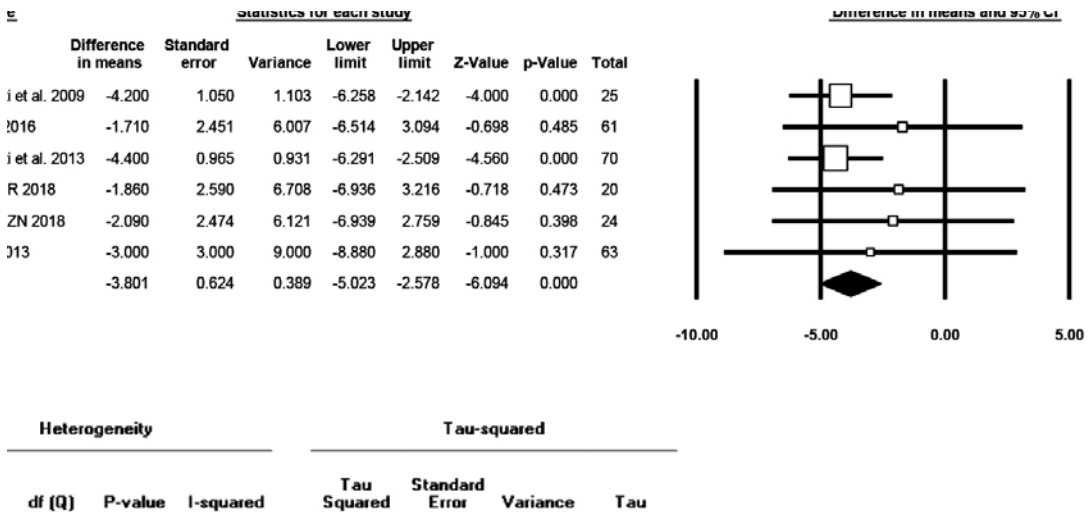
As shown in Fig. 2A, there were 5 studies (35,56-58,60) (one compared two different types of percutaneous adhesiolysis) included in this single-arm meta-analysis, and the results showed an improvement in the NRS pain scores for pain after percutaneous adhesiolysis at 3 months, on average 3.801 ($P < 0.001$).

As shown in Fig. 2B, there were 5 studies (35,56-58,60) (one compared two different types of percutaneous adhesiolysis) included in this single-arm meta-analysis, and the results showed an improvement in the ODI functionality scores after percutaneous adhesiolysis at 3 months, on average 15.039 (on 0-50 scale) ($P < 0.001$)

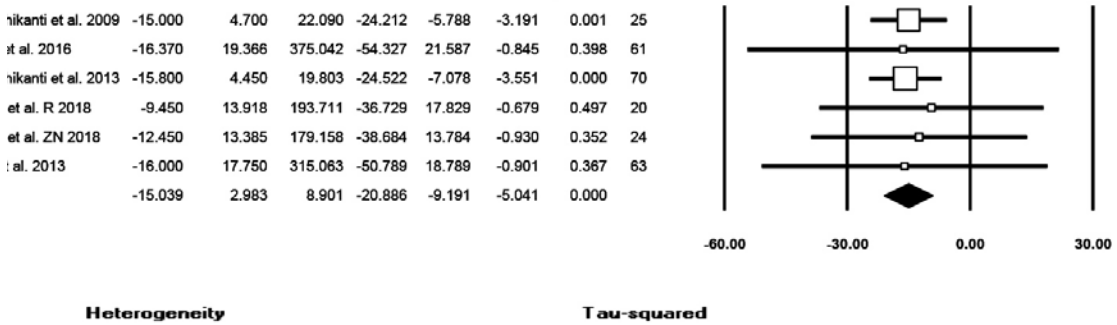
Pain and Functionality at 6 months

As shown in Fig. 3A, there were 4 studies (35,56-58) (one compared two different types of percutaneous adhesiolysis) included in this single-arm meta-analysis, and the results showed an improvement in the NRS pain scores for pain after percutaneous adhesiolysis at 6 months, on average 3.707 ($P < 0.001$).

As shown in Fig. 3B, there were 4 studies (35,56-58) (one compared two different types of percutaneous adhesiolysis) included in this single-arm meta-analysis, and the results showed an improvement in the ODI functionality scores after percutaneous adhesiolysis at 6 months, on average 14.854 (on 0-50 scale) ($P < 0.001$).



A. Change in pain levels using the Numeric Rating Scale (NRS).



B. Change in functionality scores using the Oswestry Disability Index (ODI).

Fig. 2. *Change in pain scores and functional scores using Oswestry Disability Index from baseline at 3 months in patients treated with percutaneous adhesiolysis.*

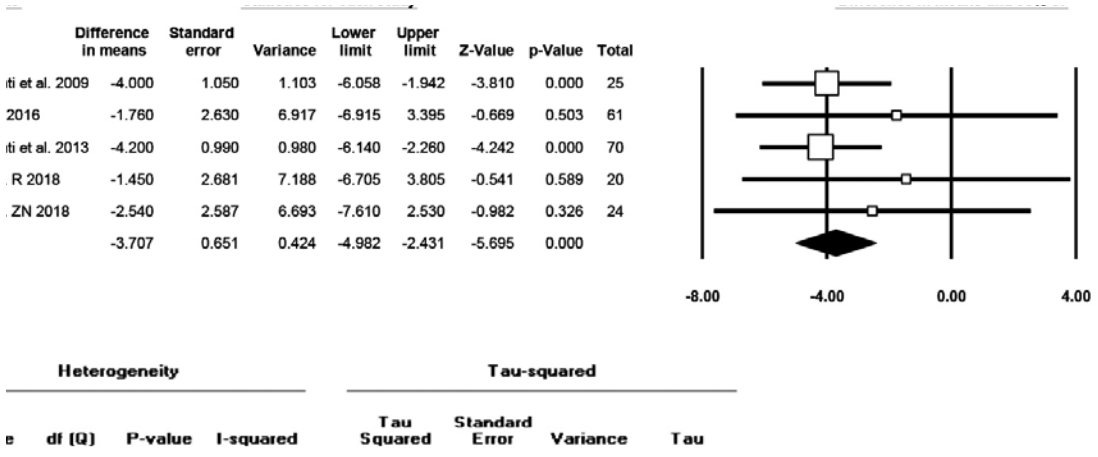
Pain and Functionality at 12 months

As shown in Fig. 4A, there were 3 studies (35,56,58) included in this single-arm meta-analysis, and the results showed an improvement in the NRS pain scores for back pain after percutaneous adhesiolysis at 12 months, on average 3.847 ($P < 0.001$).

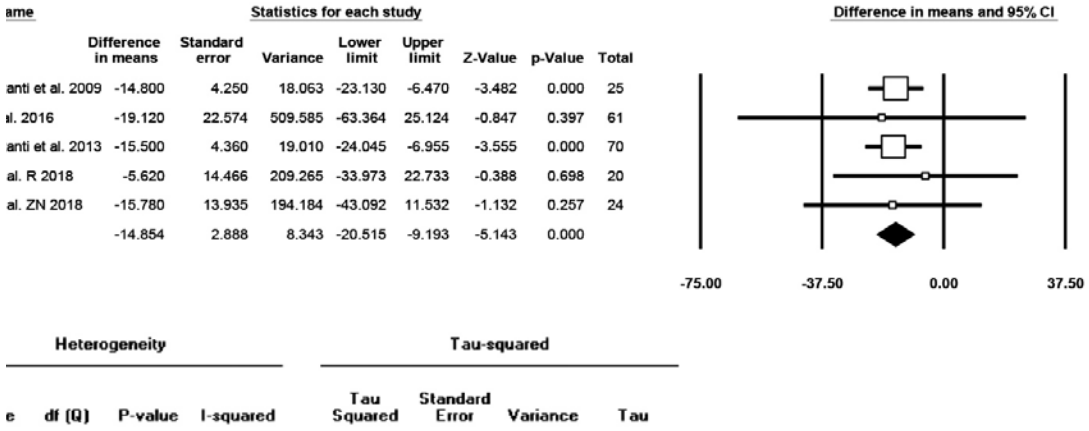
As shown in Fig. 4B, there were 3 studies (35,56,58) included in this single-arm meta-analysis, and the results showed an improvement in the ODI functionality scores after percutaneous adhesiolysis at 12 months, on average 15.394 (on 0-50 scale) ($P < 0.001$).

Assessment of Quantitative Analysis

Based on the single-arm meta-analysis, significant improvement in pain scores was observed at 3 months, 6 months, and 12 months. Similarly, improvement in functional status based on Oswestry disability scores was also observed at all 3 points of assessment. Average



A. Change in pain levels using the Numeric Rating Scale (NRS).



B. Change in functionality scores using the Oswestry Disability Index (ODI).

Fig. 3. *Change in pain scores and functional scores using Oswestry Disability Index from baseline at 6 months in patients treated with percutaneous adhesiolysis.*

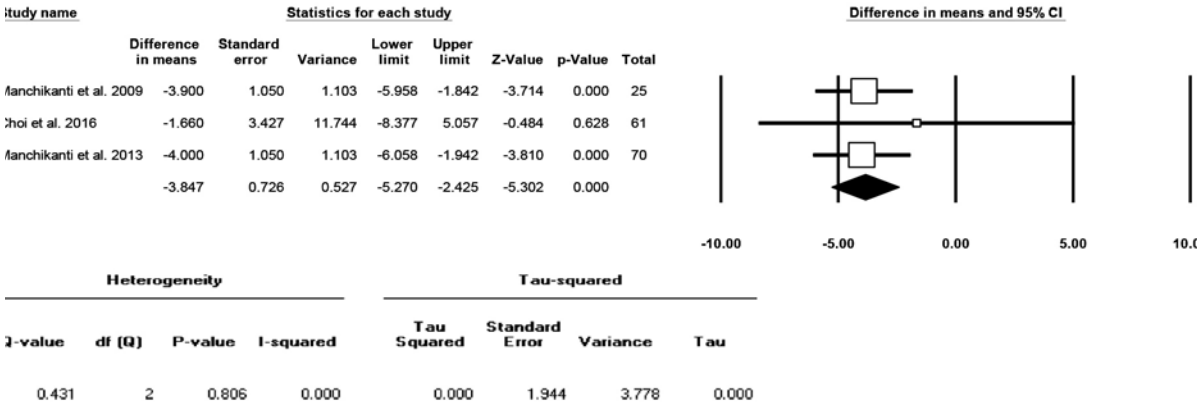
pain improvement was 3.8 at 3 months, 3.7 at 6 months, and 3.8 at 12 months. Similarly, average improvement in disability scores was on average 15 on a scale of 0-50 at 3, 6, and 12-month follow up. However, more importantly, the proportion of patients showing at least 50% improvement in pain and function was significantly higher in randomized and observational studies.

Qualitative analysis showed effectiveness of percutaneous adhesiolysis and superiority over epidural injections. With qualitative analysis, there was significant evidence of effectiveness with both RCTs and 4 observational studies. With quantitative analysis, utilizing single-arm meta-analysis, significant improvement in pain and function with percutaneous adhesiolysis was identified.

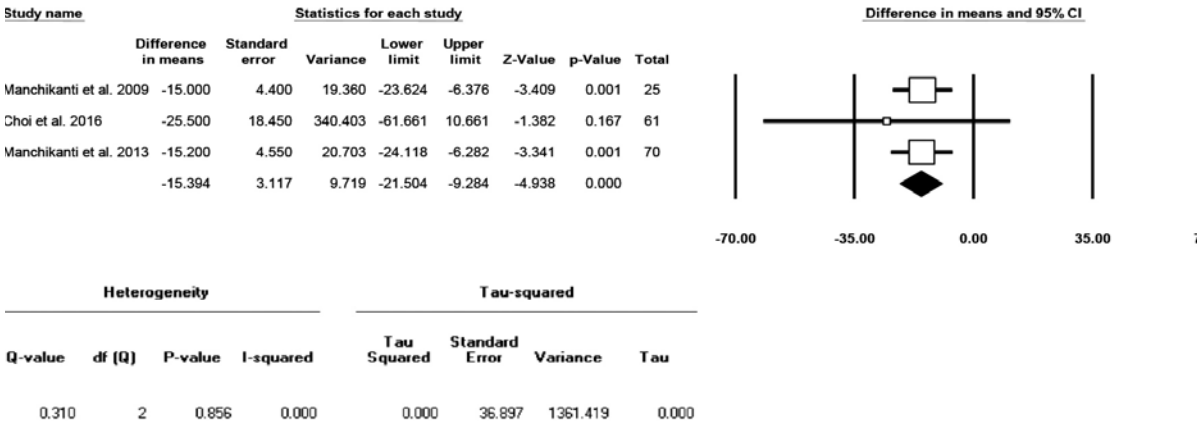
Consequently, based on the total of 6 available studies with 2 RCTs (56,57) and 4 observational studies (35,58,60,73) percutaneous adhesiolysis with targeted administration of local anesthetic and steroids with or without hypertonic sodium chloride solution and with or without balloon inflation showed significant improvement with Level II or moderate evidence.

Discussion

Analysis of effectiveness of percutaneous adhesiolysis in managing central spinal stenosis showed



A. **Change in pain scores using the Numeric Rating Scale (NRS).**



B. **Change in functionality scores using the Oswestry Disability Index (ODI).**

Fig. 4. *Change in pain scores and functional scores using Oswestry Disability Index from baseline at 12 months in patients treated with percutaneous adhesiolysis*

Level II or moderate evidence in the present systematic review and meta-analysis with inclusion of 2 RCTs (56,57) and 4 observational studies (35,58,60,73) with at least 12 months of appropriate outcomes available. The primary outcome or hard endpoint was the proportion of patients with 50% pain relief and improvement in functionality, whereas secondary outcome measures, or soft endpoints, were pain relief and/or improvement in functionality. The positive results were observed from all the studies included in this analysis, even though balloon inflated catheters showed superior results compared to catheter adhesiolysis. Among the randomized trials, one randomized trial (56) assessing response rate based on significant improvement of 50% pain relief and functional status has shown success rate of 76% at 12 months, compared to 4% in the caudal epidural group. The second RCT (57) with only 6 month follow-up available comparing catheter-based adhesiolysis with inflatable balloon catheter showed superior results with balloon inflatable catheter. Further, among the observational studies, one study followed the patients for 24 months with a 71% improvement rate. Surprisingly enough, in this systematic review, superior results were observed in appropriately conducted long-term studies (35,56). Single arm meta-analysis also showed significant improvement from baseline with 38% improvement with pain relief and 30% improvement with functional status overall combining all the studies.

Further, the available data shows superior results when significant improvement was utilized as the primary outcome parameter at 12 months as well as 24 months in over 70% of the patients.

Symptomatic lumbar spinal stenosis is a debilitating condition and challenging for appropriate successful treatment. While surgical intervention is performed commonly, the failure rate is high. The present evidence does not show any significant difference between conservative and surgical management (4-6,10,11,46,49). In contrast, epidural injections and percutaneous adhesiolysis have been shown to be cost effective and clinically effective and also with favorable cost utility analysis (33,34,37,62-65). Even then, the literature related to percutaneous adhesiolysis is sparse, with no systematic reviews performed specific to effectiveness of percutaneous adhesiolysis in central spinal stenosis. Consequently, this is the first systematic review that has demonstrated positive results with moderate evidence for its effectiveness.

Percutaneous epidural neurolysis, adhesiolysis, neuroplasty, or lysis of adhesions are interventional pain management techniques that have emerged over approximately the last 30 years, mainly in managing post lumbar surgery syndrome and subsequently followed by central spinal stenosis and also in recent years, recalcitrant disc herniation (36,76). While the primary goal of this procedure in post lumbar surgery syndrome is lysis of fibrous adhesions that may prevent free movement of structures in the intervertebral foramina and in the bony vertebral canal, in central spinal stenosis the mechanism is related to targeted delivery and lysis of fibrous adhesions developed in spinal stenosis. Thus, adhesiolysis facilitates application of medication to structures believed to be the source of pain, and provides targeted application of local anesthetics, corticosteroids, and other agents. A systematic review of analysis of evidence of percutaneous adhesiolysis in various conditions including spinal stenosis (36) showed significant evidence for the role of lysis of adhesions in patients with central spinal stenosis. In the present analysis, as in the previous analysis, the majority of the patients studied were non-responsive to epidural injections and all types of conservative modalities. The majority of these patients without percutaneous adhesiolysis undergo placement of an interspinous process device, with Superion, MILD®, or surgical interventions (3,4,6,7,10,47-54).

The analysis of the data from this systematic review utilizing qualitative and quantitative analysis with single-arm analysis provides not only the evidence, but also insight into the effectiveness literature. Further, it also provides the evidence of the importance of understanding the technique, drugs utilized, and proper analysis of technical components. In addition, this analysis has shown the best results in patients when they were analyzed for hard end points with significant improvement with at least 50% improvement in pain and functional status. Single-arm analysis also showed in improvement in soft end points of 38% in overall pain scores and 30% in disability scores. In recent years, the importance of single-arm analysis has been emphasized with multiple studies showing significant evidence with single-arm meta-analysis, when dual-arm analysis provides lack of evidence or equal evidence with a control group (31,44,77). In recent years, there has been a large volume of research conducted and published, often with divergent and conflicting results, leading to extensive debate in interventional pain management (31,36,38,43,44,61,77-79). Differences in conclusions may be the product of individual preference of the investigator, experience, lack of clinical experience, overenthusiastic academic performance and publication, interest, publication of negative studies, conflicts of interest, and confluence of interest (31,36,43,61,80-88). In addition, mass production of literature leads not only to conflicting systematic review and meta-analysis (89-93), but also with the creation of redundancy and reduced value and sustainability of evidence-based medicine and leads to basic questions about evidence-based medicine itself (89-97). Thus, this systematic review provides appropriate evidence synthesis and conclusions based on utilization of qualitative and quantitative analysis with single-arm analysis, showing moderate or Level II evidence for percutaneous adhesiolysis in the treatment of central spinal stenosis.

Conclusion

This systematic review utilizing appropriate reporting methodology, qualitative and quantitative analysis utilizing single-arm meta-analysis with incorporation of 2 RCTs and 4 observational studies demonstrated Level II, or moderate evidence, for the effectiveness of percutaneous adhesiolysis in managing pain of central spinal stenosis. Future studies will provide more data and understanding for clinicians on the role of percutaneous adhesiolysis in patients who have pain related to central spinal stenosis.

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Appendix Table 1. *Sources of risk of bias and Cochrane Review rating system.*

Bias Domain	Source of Bias		Possible Answers
Selection	(1) Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, preordered sealed envelopes, sequentially-ordered vials, telephone call to a central office, and preordered list of treatment assignments.	Yes/No/Unsure
		Examples of inadequate methods are: alternation, birth date, social insurance/ security number, date in which they are invited to participate in the study, and hospital registration number.	
Selection	(2) Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/Unsure
Performance	(3) Was the patient blinded to the intervention?	Index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/Unsure
Performance	(4) Was the care provider blinded to the intervention?	Index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/Unsure
Detection	(5) Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for each primary outcome separately. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or:	Yes/No/Unsure
		• for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes"	
		• for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination	
		• for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome	
		• for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., cointerventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes"	
		• for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data	
Attrition	(6) Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/Unsure
Attrition	(7) Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of noncompliance and cointerventions.	Yes/No/Unsure

Appendix Table 1 (cont.). *Sources of risk of bias and Cochrane Review rating system.*

Bias Domain	Source of Bias		Possible Answers
Reporting	(8) Are reports of the study free of suggestion of selective outcome reporting?	All the results from all prespecified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/Unsure
Selection	(9) Were the groups similar at baseline regarding the most important prognostic indicators?	Groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/Unsure
Performance	(10) Were cointerventions avoided or similar?	If there were no cointerventions or they were similar between the index and control groups.	Yes/No/Unsure
Performance	(11) Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered for several sessions; therefore it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/Unsure
Detection	(12) Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all primary outcome measures.	Yes/No/Unsure
Other	(13) Are other sources of potential bias unlikely?	Other types of biases. For example: • When the outcome measures were not valid. There should be evidence from a previous or present scientific study that the primary outcome can be considered valid in the context of the present. • Industry-sponsored trials. The conflict of interest (COI) statement should explicitly state that the researchers have had full possession of the trial process from planning to reporting without funders with potential COI having any possibility to interfere in the process. If, for example, the statistical analyses have been done by a funder with a potential COI, usually "unsure" is scored.	Yes/No/Unsure

Source: Furlan AD, Malmivaara A, Chou R, Maher CG, Deyo RA, Schoene M, Bronfort G, van Tulder MW; 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; 40:1660-1673 (69).

Appendix Table 2. *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.*

		Scoring
I.	TRIAL DESIGN AND GUIDANCE REPORTING	
1.	CONSORT or SPIRIT	
	Trial designed and reported without any guidance	0
	Trial designed and reported utilizing minimum criteria other than CONSORT or SPIRIT criteria or trial was conducted prior to 2005	1
	Trial implies it was based on CONSORT or SPIRIT without clear description with moderately significant criteria for randomized trials or the trial was conducted before 2005	2
	Explicit use of CONSORT or SPIRIT with identification of criteria or trial conducted with high level reporting and criteria or conducted before 2005	3
II.	DESIGN FACTORS	
2.	Type and Design of Trial	
	Poorly designed control group (quasi selection, convenient sampling)	0
	Proper active-control or sham procedure with injection of active agent	2
	Proper placebo control (no active solutions into active structures)	3
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology/radiology/ortho, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 50 participants in the study without appropriate sample size determination	0
	Sample size calculation with less than 25 patients in each group	1
	Appropriate sample size calculation with at least 25 patients in each group	2
	Appropriate sample size calculation with 50 patients in each group	3
6.	Statistical Methodology	
	None or inappropriate	0
	Appropriate	1
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	0
	Clearly identified mixed population	1
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	2
7b.	For facet or sacroiliac joint interventions:	
	No diagnostic blocks	0
	Selection with single diagnostic blocks	1
	Selection with placebo or dual diagnostic blocks	2
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1

Appendix Table 2 (cont.). *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.*

		Scoring
8.	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or 12 weeks for epidural or facet joint procedures, etc. and 6 months for intradiscal procedures and implantables	0
	3 to 6 months for epidural or facet joint procedures, etc., or 1 year for intradiscal procedures or implantables	1
	6 months to 17 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	2
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	3
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Analysis of all Randomized Participants in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized participants	1
	All participants included with or without intent-to-treat analysis	2
13.	Description of Drop Out Rate	
	No description of dropouts, despite reporting of incomplete data or ≥ 20% withdrawal	0
	Less than 20% withdrawal in one year in any group	1
	Less than 30% withdrawal at 2 years in any group	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	Groups dissimilar with significant influence on outcomes with or without appropriate randomization and allocation	0
	Groups dissimilar without influence on outcomes despite appropriate randomization and allocation	1
	Groups similar with appropriate randomization and allocation	2
15.	Role of Co-Interventions	
	Co-interventions were provided but were not similar in the majority of participants	0
	No co-interventions or similar co-interventions were provided in the majority of the participants	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0

Appendix Table 2 (cont.). *Item checklist for assessment of randomized controlled trials of IPM techniques utilizing IPM – QRB.*

		Scoring
16.	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High quality randomization (Computer generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call, pre-ordered list of treatment assignments, etc.)	2
VI.	ALLOCATION CONCEALMENT	
17.	Concealed Treatment Allocation	
	Poor concealment of allocation (open enrollment) or inadequate description of concealment	0
	Concealment of allocation with borderline or good description of the process with probability of failure of concealment	1
	High quality concealment with strict controls (independent assignment without influence on the assignment sequence)	2
VII.	BLINDING	
18.	Patient Blinding	
	Patients not blinded	0
	Patients blinded adequately	1
19.	Care Provider Blinding	
	Care provider not blinded	0
	Care provider blinded adequately	1
20.	Outcome Assessor Blinding	
	Outcome assessor not blinded or was able to identify the groups	0
	Performed by a blinded independent assessor with inability to identify the assignment-based provider intervention (i.e., subcutaneous injection, intramuscular distant injection, difference in preparation or equipment use, numbness and weakness, etc.)	1
VIII.	CONFLICTS OF INTEREST	
21.	Funding and Sponsorship	
	Trial included industry employees	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only with supporting entity unrelated to industry	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
22.	Conflicts of Interest	
	None disclosed with potential implied conflict	0
	Marginally disclosed with potential conflict	1
	Well disclosed with minor conflicts	2
	Well disclosed with no conflicts	3
	Hidden conflicts with poor disclosure	–1
	Misleading disclosure with conflicts	–2
	Major impact related to conflicts	–3
TOTAL		48

Appendix Table 3. *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

		Scoring
I.	STUDY DESIGN AND GUIDANCE REPORTING	
1.	STROBE or TREND Guidance	
	Case Report/Case Series	0
	Study designed without any guidance	1
	Study designed with minimal criteria and reporting with or without guidance	2
	Study designed with moderately significant criteria or implies it was based on STROBE or TREND without clear description or the study was conducted before 2011 or similar criteria utilized with study conducted before 2011	3
	Designed with high level criteria or explicitly uses STROBE or TREND with identification of criteria or conducted prior to 2011	4
II.	DESIGN FACTORS	
2.	Study Design and Type	
	Case report or series (uncontrolled – longitudinal)	0
	Retrospective cohort or cross-sectional study	1
	Prospective cohort case-control study	2
	Prospective case control study	3
	Prospective, controlled, nonrandomized	4
3.	Setting/Physician	
	General setting with no specialty affiliation and general physician	0
	Specialty of anesthesia/PMR/neurology, etc.	1
	Interventional pain management with interventional pain management physician	2
4.	Imaging	
	Blind procedures	0
	Ultrasound	1
	CT	2
	Fluoro	3
5.	Sample Size	
	Less than 100 participants without appropriate sample size determination	0
	At least 100 participants in the study without appropriate sample size determination	1
	Sample size calculation with less than 50 patients in each group	2
	Appropriate sample size calculation with at least 50 patients in each group	3
	Appropriate sample size calculation with 100 patients in each group	4
6.	Statistical Methodology	
	None	0
	Some statistics	1
	Appropriate	2
III.	PATIENT FACTORS	
7.	Inclusiveness of Population	
7a.	For epidural procedures:	
	Poorly identified mixed population	1
	Poorly identified mixed population with large sample (≥ 200)	2
	Clearly identified mixed population	3
	Disorders specific trials (i.e. well defined spinal stenosis and disc herniation, disorder specific, disc herniation or spinal stenosis or post surgery syndrome)	4

Appendix Table 3 (cont.). *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

		Scoring
7b.	For facet or sacroiliac joint interventions:	
	No specific selection criteria	1
	No diagnostic blocks based on clinical symptomatology	2
	Selection with single diagnostic blocks	3
	Selection with placebo or dual diagnostic blocks	4
8.	Duration of Pain	
	Less than 3 months	0
	3 to 6 months	1
	> 6 months	2
9.	Previous Treatments	
	Conservative management including drug therapy, exercise therapy, physical therapy, etc.	
	Were not utilized	0
	Were utilized sporadically in some patients	1
	Were utilized in all patients	2
10.	Duration of Follow-up with Appropriate Interventions	
	Less than 3 months or less for epidural or facet joint procedures, etc., and 6 months for intradiscal procedures and implantables	1
	3-6 months for epidural or facet joint procedures, etc., or one year for intradiscal procedures or implantables	2
	6-12 months for epidurals or facet joint procedures, etc., and 2 years or longer for discal procedures and implantables	3
	18 months or longer for epidurals and facet joint procedures, etc., or 5 years or longer for discal procedures and implantables	4
IV.	OUTCOMES	
11.	Outcomes Assessment Criteria for Significant Improvement	
	No descriptions of outcomes OR < 20% change in pain rating or functional status	0
	Pain rating with a decrease of 2 or more points or more than 20% reduction OR functional status improvement of more than 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
	Pain rating with a decrease of 3 or more points or more than 50% reduction OR functional status improvement with a 50% or 40% reduction in disability score	2
	Significant improvement with pain and function ≥ 50% or 3 points and 40% reduction in disability scores	4
12.	Description of Drop Out Rate	
	No description despite reporting of incomplete data or more than 30% withdrawal	0
	Less than 30% withdrawal in one year in any group	1
	Less than 40% withdrawal at 2 years in any group	2
13.	Similarity of Groups at Baseline for Important Prognostic Indicators	
	No groups or groups dissimilar with significant influence on outcomes	0
	Groups dissimilar without significant influence on outcomes	1
	Groups similar	2
14.	Role of Co-Interventions	
	Dissimilar co-interventions or similar co-interventions in some of the participants	1

Appendix Table 3 (cont.). *IPM checklist for assessment of nonrandomized or observational studies of IPM techniques utilizing IPM-QRBNR.*

		Scoring
14.	No co-interventions or similar co-interventions in majority of the participants	2
V.	ASSIGNMENT	
15.	Method of Assignment of Participants	
	Case report/case series or selective assignment based on outcomes or retrospective evaluation based on clinical criteria	1
	Prospective study with inclusion without specific criteria	2
	Retrospective method with inclusion of all participants or random selection of retrospective data	3
	Prospective, well-defined assignment of methodology and inclusion criteria (quasi randomization, matching, stratification, etc.)	4
VI.	CONFLICTS OF INTEREST	
16.	Funding and Sponsorship	
	Trial included industry employees with or without proper disclosure	-3
	Industry employees involved; high levels of funding with remunerations by industry or an organization funded with conflicts	-3
	Industry or organizational funding with reimbursement of expenses with some involvement or no information available	0
	Industry or organization funding of expenses without involvement	1
	Funding by internal resources only	2
	Governmental funding without conflict such as NIH, NHS, AHRQ	3
TOTAL MAXIMUM		48

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