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Meta-Analysis

Transforaminal Epidural Steroid Injections: A Systematic Review and Meta-Analysis of Efficacy and Safety

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Background: Transforaminal epidural injections have been used since the late 1990s to treat lumbar radicular pain. They have been the subject of considerable attention, with varying conclusions from systematic reviews as to their efficacy. Transforaminal injections have been associated with rare but major complications. Further, the use of transforaminal injections has increased since the passage of the Affordable Care Act. Finally, with the SARS-CoV-2 pandemic, there has been heightened concern regarding the risk associated with steroid injections.

Objectives: To evaluate and update the effectiveness of transforaminal injections for 4 indications: radicular pain; from spinal stenosis; from failed back surgery syndrome; and for axial low back pain; and to evaluate the safety of the procedure.

Study Design: A systematic review and meta-analysis of the efficacy of transforaminal injections.

Methods: The available literature on transforaminal injections was reviewed and the quality assessed. The level of evidence was classified on a 5-point scale based on the quality of evidence developed by the US Preventive Services Task Force (USPSTF) and modified by the American Society of Interventional Pain Physicians (ASIPP). Data sources included relevant literature from 1966 to April 2020, and manual searches of the bibliographies of known primary and review articles. Pain relief and functional improvement were the primary outcome measures. A minimum of 6 months pain relief follow-up was required.

Results: For this systematic review, 66 studies were identified. Eighteen randomized controlled trials met the inclusion criteria. No observational studies were included. Eleven randomized controlled trials dealt with various aspects of transforaminal injections for radicular pain owing to disc herniation. Based on these studies, there is Level 1 evidence supporting the use of transforaminal injections for radicular pain owing to disc herniation. A meta-analysis showed that at both 3 and 6 months, there was highly statistically significant improvement in both pain and function with both particulate and nonparticulate steroids. For radicular pain from central stenosis there is one moderate quality study, with Level IV evidence. For radicular pain caused by failed back surgery syndrome there is one moderate quality study, with Level IV evidence. For radicular pain from foraminal stenosis and for axial pain there is Level V evidence, opinion-based/consensus, supporting the use of transforaminal injections. Transforaminal injections are generally safe. However, they have been associated with major neurologic complications related to cord infarct. Causes other than intraluminal injection of particulates appear to be at play. The use of an infraneural approach and of blunt needles appear to offer the greatest patient safety. Because of concern over the role of particulate steroids, multiple other injectates have been evaluated, including nonparticulate steroids, tumor necrosis factor alpha (TNF-α) inhibitors, and local anesthetics without steroids. No injectate has been proven superior. If there is concern about immunosuppression because of risk of COVID-19 infection, either the lowest possible dose of steroid or no steroid should be used.

Limitations: The study was limited by the paucity of literature for some indications.

Conclusions: There is Level I evidence for the use of transforaminal injections for radicular pain from disc herniations.

Key words: Disc herniation, spinal pain, radicular pain, epidural steroid injection, transforaminal injection, spinal stenosis, post lumbar surgery syndrome, axial low back pain

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Epidural injections have been used since about 1900 for the treatment of low back and lower extremity pain, with steroids added to local anesthetics in about 1950 (1-4). The epidural space can be entered by 3 approaches: caudal, interlaminar, and transforaminal. Multiple systematic reviews have evaluated the efficacy and safety of epidural injections (5-23). These reviews have famously offered differing, even contradictory, conclusions regarding the role of epidural steroid injections. They have also varied markedly in the indications and approaches evaluated.

The Koes et al (5) 1995 review, in which none of the studies reported image guidance, found that one-half of the accepted studies reported positive results and one-half negative.

Luijsterburg et al (6), in 2007, looked at randomized controlled trials (RCTs) evaluating conservative treatment, including injections, for radicular pain, concluding lack of efficacy from the procedure.

Novak and Nemeth (7) assessed the frequency at which epidural injections should be performed. They found that the evidence available did not provide any guidance as to when repeat injections should be performed.

A Cochrane review by Staal et al (8) in 2009 found 18 studies evaluating injection therapy, including epidural injections for chronic low back pain. Staal et al (8) concluded that there was insufficient evidence to support injection therapy, although it was possible that subgroups existed who might benefit. Regarding epidural injections, the review was confounded by the evaluation of both high- and low-quality studies, the interpretation of local anesthetic injections as being placebos, and by the conclusion that the lack of difference in efficacy between 2 different local anesthetics documented lack of efficacy.

In 2009, Buenaventura et al (21) looked specifically at transforaminal injections for low back and lower extremity pain, reporting both short- and long-term benefit for these indications, with limited evidence supporting transforaminal injections for post lumbar surgery syndrome.

Chou and Huffman (20) produced an analysis of the treatment of low back pain for the American Pain Society in 2007, with the conclusion that the evidence was mixed for transforaminal injections for low back pain with sciatica. The same evidence was critically reassessed by the American Society of Interventional Pain Physicians (ASIPP), with the conclusion that the evidence for treating lumbar nerve root pain was fair, using a 3-point scale (24).

Quraishi (22) evaluated lumbar transforaminal injections for lumbar radiculopathy. He found that the injections provided pain relief but not increased function. He also found that transforaminal injections with local anesthetic but no steroids provided up to 12 months relief.

Manchikanti et al (9) presented a systematic review looking specifically at transforaminal injections for low back and lower extremity pain in 2012. The study looked at disc herniation, spinal stenosis, discogenic pain, and post lumbar surgery syndrome. The evidence, using a 3-point scale of good, fair, and poor, was good for transforaminal injections with steroids for disc herniation, fair for local anesthetics alone for disc herniation, and fair for local anesthetics and steroids for spinal stenosis. The evidence was poor for axial low back pain and post lumbar surgery syndrome.

Parr et al (10) looked at caudal epidural injections in 2012. The study showed good evidence for disc herniation treated with local anesthetic and steroids, whereas there was fair evidence for local anesthetics alone for treating pain from disc herniations. The evidence was fair for axial or discogenic pain, spinal stenosis, and post-surgery syndrome.

In 2014, Shamliyan et al (11) published a review for a purveyor of proprietary guidelines of epidural injections for radicular pain. The study found no difference between injections with local anesthetics and steroids versus local anesthetics alone. The study did not recommend the routine use of epidural injections. The ASIPP guidelines were criticized because other societies did not evaluate them.

Chang Chien et al (13) compared interlaminar versus transforaminal injections for radicular pain, with the conclusion that both approaches were equally effective.

Manchikanti et al (14) looked specifically at the role of epidural injections in treating axial low back pain, with no radicular component. The study found Level II, on a I to V scale, supporting the use of caudal and interlaminar injections in these patients. The study also found limited evidence to support the role of surgery.

Chou et al (16), publishing in Annals of Internal Medicine in 2015, looked at epidural injections for radicular pain and for spinal stenosis, finding short-term benefit for radiculopathy and limited support for epidurals in spinal stenosis.

Manchikanti et al (18) responded to Chou et al, performing a systematic review of epidural injections

for radicular pain and for spinal stenosis. They found lidocaine with or without steroids to be significantly effective, whereas sodium chloride or bupivacaine were not. These findings differed from Chou et al primarily because Chou et al classified active controls as placebos.

In 2015, Kaye et al (17) looked at epidural injections for chronic spinal pain. Using a 5-point scale, they found Level II evidence for all 3 approaches for radicular pain. There was Level II evidence for caudal and interlaminar epidural injections, with Level III evidence for transforaminal injections for spinal stenosis.

In 2018, Lee et al (19) revisited the question of transforaminal versus interlaminar injections for lumbar disc herniation. Their study found significantly better short-term relief from transforaminal injections and slightly better long-term pain relief, and short- and long-term improvement in disability from transforaminal injections compared with interlaminar injections.

Smith et al (23) published the most recent systematic review of transforaminal epidural steroid injections in 2020, focusing on radicular pain. They found that there was strong evidence supporting the use of lumbar transforaminal epidural injections for radicular pain owing to disc herniation, but there was a lack of high-quality evidence supporting their use for spinal stenosis.

Thus there continues to be on-going disagreement about the role of lumbar epidural injections.

The utilization of lumbar epidural injections has changed markedly over time (25). From 2000 until 2009, the number of epidural injections of all types to Medicare beneficiaries increased at an annual rate of 7.3%. From 2009 to 2018, there was an annual decline of 2.5%. These changes coincide with the signing of the Affordable Care Act in March 2010. However, when interlaminar/caudal injections are compared with transforaminal injections, there has been a marked percentage decrease in the number of interlaminar/caudal injections (4.7%) compared with a small percentage decrease in the number of transforaminal injections (1.1%).

Thus although there has been a decrease in the number of epidural injections since the adoption of the Affordable Care Act, there has also been a shift from caudal and interlaminar injections to transforaminal injections.

Lumbar transforaminal epidural injections have also been the focus of safety concerns. The occurrence of serious neurologic complications after epidural steroid injections was sufficient to cause the US Food and Drug Administration (FDA) to convene a meeting on this topic in 2014 (26). Lumbar transforaminal injections in particular have been associated with complications.

We are conducting this review of the effectiveness of lumbar transforaminal epidural steroid injections in treating radicular pain, pain from spinal stenosis, pain after lumbar surgery, and axial low back pain because:

- There is ongoing discussion as to whether lumbar epidural steroid injections are effective in treating these 4 indications.
- There has been a shift from caudal to transforaminal procedure since the implementation of the Affordable Care Act.
- There has been significant concern regarding the risks associated with lumbar transforaminal injections.
- There has been, since the advent of the SARS-CoV-2 pandemic, concern over the role of steroids in epidural injections.

For these reasons, the focus is on transforaminal rather than interlaminar or caudal injections.

This systematic review will reassess all the literature on therapeutic transforaminal epidural steroid injections up to April 2020, including new literature since the last reviews. This review will focus on radicular pain, post lumbar surgery syndrome, spinal stenosis, and axial low back pain.

Methods

The methodology utilized in this systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials and observational studies (27-42).

Criteria for Considering Studies for this Review

Types of Studies

- RCTs
- Nonrandomized observational studies
- Case reports and reviews were evaluated for adverse effects

Types of Patients

Patients receiving transforaminal epidural injections, with or without steroids, for herniated nucleus pulposus/radicular pain, pain from spinal stenosis, pain after lumbar surgery, and axial low back pain not of facet or sacroiliac origin.

Types of Interventions

Lumbar transforaminal injections with local anesthetics with or without steroids.

Types of Outcome Measures

The primary outcome parameter was pain relief.

The secondary outcome measures were functional status improvement, change in psychological status, or a reduction in either opioid use or reliance on health care interventions.

Literature Search

Searches were performed from the following sources, limited to articles published in English:

1. PubMed from 1966
   https://www.ncbi.nlm.nih.gov/pubmed
2. Cochrane Library
   https://www.cochranelibrary.com/
3. Google Scholar
   https://scholar.google.com/
4. Previous systematic reviews
5. Clinical Trials
   https://clinicaltrials.gov/
6. Communication with investigators active in the field.
7. Bibliographies of reviewed articles were also examined.

The search period was from 1966 through April 2020.

Search Strategy

The following search terms were used in PubMed: ((((((((((((chronic low back pain) OR disc herniation) OR discogenic pain) OR herniated lumbar discs) OR nerve root compression) OR lumbosciatic pain) OR postlaminectomy) OR lumbar surgery syndrome) OR radicular pain) OR radiculitis) OR sciatica) OR spinal stenosis) AND ((((((((epidural injection) OR epidural steroid) OR epidural perineural injection) OR nerve root blocks) OR periradicular infiltration) OR transforaminal injection) OR corticosteroid) OR methylprednisolone) AND ((meta-analysis [pt] OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] 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]) NOT (animals [mh] NOT human [mh])))

Data Collection and Analyses

Two review authors independently, in an unblinded standardized manner, developed search criteria, searched for relevant literature, and selected the manuscripts.

Selection of Studies

Two review authors screened the abstracts of all identified studies against the inclusion criteria. All articles with possible relevance were then retrieved in full text for comprehensive assessment of internal validity, quality, and adherence to inclusion criteria.

Inclusion and Exclusion Criteria

Only RCTs and observational studies with at least 6 months follow-up, with statistical analysis, and with at least 50 patients in the study or with 25 patients in a group were included. Reports without appropriate diagnoses, nonsystematic reviews, book chapters, and case reports were excluded.

For any condition, if there were more than 5 randomized trials, nonrandomized or observational studies were not utilized.

Methodological Quality or Validity Assessment

The quality of each individual article used in this analysis was assessed by:

1. Cochrane Review criteria (38) (Appendix Table 1), and
2. (ASIPP) Interventional Pain Management techniques—Quality Appraisal of Reliability and Risk of Bias Assessment (IPM–QRB) for Randomized Trials (43) (Appendix Table 2), and
3. ASIPP Interventional Pain Management Techniques–Quality Appraisal of Reliability and Risk of Bias Assessment for Nonrandomized Studies (IPM–QRBNR) for Nonrandomized and Observational Studies (44).

Utilizing Cochrane review criteria, studies meeting the inclusion criteria with at least 8 of 12 criteria were considered high quality, and 5 to 7 were considered moderate quality. Those meeting criteria of less than 5 were considered as low quality and were excluded.

Based on ASIPP criteria for randomized trials and nonrandomized studies, the studies meeting the inclusion criteria scoring of 32 to 48 were considered high-quality trials; studies with scores between 25 and 31 were considered moderate quality; studies scoring less than 25 were considered low quality and were excluded.

Data Extraction and Management

Methodologic quality assessment was performed by the authors with groups of 2 authors reviewing multiple manuscripts. 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. Any discrepancies in the methodologic quality assessment were evaluated by a third reviewer and settled by consensus.

If there was conflict of interest with a reviewed manuscript, the involved author(s) did not review the manuscript for methodologic quality assessment.

Meta-Analysis

If the literature search provided at least 3 randomized trials meeting the inclusion criteria and they are clinically homogenous for each modality and condition evaluated, a meta-analysis was performed.

Single-Arm Meta-Analysis

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

For pain and functionality improvement data, the studies were reported as the mean differences with 95% confidence intervals.

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

Outcome Measurements

Previously, the consensus was that at least a 2-point change on a 0 to 10-point pain scale was necessary to document a clinically meaningful change. The current consensus is that clinically meaningful change requires the more rigorous standard of 50% pain relief (30,31,38,43-51).

This study will define clinically meaningful pain relief as a 50% reduction from baseline. Clinically meaningful functional status improvement is 40% or more.

Short-term efficacy is defined as less than 6 months; long-term efficacy is defined as 6 months or longer.

Grading of Evidence

The grading of the evidence was performed using ASIPP's modification of the US Preventive Services Task Force's (USPSTF) and other criteria (52-58).

Table 1 shows ASIPP's method of rating evidence, ranging from Level I, multiple RCTs, as the strongest level of evidence to Level V, consensus (58).

Results

Table 2 shows a flow diagram of study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (59).

There were 66 trials considered for inclusion (60-125). Noteworthy among the articles that were not considered for inclusion is the Verheijen et al (126) study protocol for a comparison of transforaminal epidural steroid injections and conservative care for sciatica. When completed, this study will be a useful addition to the literature.

Appendix Table 3, List of excluded randomized and nonrandomized studies, shows the reasons for exclusion.

Table 3 illustrates the characteristics of the trials considered for inclusion.

Table 1. *ASIPP qualitative modified approach to grading of evidence (58).*

Level I	Strong	Evidence obtained from multiple relevant high-quality RTCs
Level II	Moderate	Evidence obtained from at least one relevant high-quality RTC or multiple relevant moderate- or low-quality RTCs
Level III	Fair	Evidence obtained from at least one relevant moderate or low-quality RTC 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

Table 2. *Flow of study selection.*

Computerized and manual search of the literature	797
Excluded by title	665
Potential articles	134
Abstracts reviewed	134
Abstracts excluded	68
Full manuscripts reviewed	66
Manuscripts excluded	40
Manuscripts included	26
RCTs	18
Observational studies	8

Table 3. *Characteristics of included randomized trials and observational studies.*

Study/Indications Evaluated (RADIC/ SS/PLLS/LBP)	Number of Patients	Treatment vs. Comparator	Length of Follow-Up	Outcome Parameters	Comments
RCTs					
Wei et al. 2020 (63) SS	90	TF injections, 30 TNF-α, 30 steroid, 30 lidocaine only	6 months	VAS, ODI	Better improvement with TNF-α
De et al. 2020 (67) RADIC	50	TF with bupivacaine, TF with bupivacaine plus pulsed radiofrequency ablation of the DRG	6 months	VAS, ODI	Greater amount and duration of improvement with pulsed radiofrequency
Makkar et al. 2019 (65) RADIC	65	TF, midline IL, and parasagittal IL	6 months	VAS, modified ODI	Greater improvement with TF and parasagittal IL than midline IL
Pandey 2016 (71) RADIC	140	TF, IL, caudal	12 months	JOA Score	All 3 routes provided relief, with more TF patients getting relief
Kamble et al. 2016 (115) RADIC	90	30 TF, 30 IL, 30 caudal	12 months	VAS, ODI	TF > IL or caudal at 1 and 6 months
Denis et al. 2015 (75) RADIC	56	TF betamethasone vs. dexamethasone	6 months	VAS, ODI	No difference between particulate and nonparticulate steroids
Ghai et al. 2014 (78) RADIC	62	30 TF vs. 32 IL	12 months	VAS, RMDQ	TF = IL
Kennedy et al. 2014 (81) RADIC	78	TF 41 dexamethasone vs. 37 triamcinolone	6 months	NRS, ODI	No difference between nonparticulate and particulate steroids
Manchikanti et al. 2014 (77) RADIC	120	60 1.5 mL 1% lidocaine with 0.5 mL saline vs. 60 1.5 mL 1% lidocaine with 0.5 mL (3 mg) betamethasone	24 months	NRS, ODI	Lidocaine with or without steroid equally effective
Cohen et al. 2012 (83) RADIC	84	TF bupivacaine with steroids, etanercept, or saline 2.5 mL	6 months	NHRS, ODI, GPE Only patients with > 50% relief and positive GPE were seen at 3 and 6 months	Local anesthetic and steroids were more effective and local anesthetics alone or with etanercept
Rados et al. 2011 (88) RADIC	64	32 TF (40 mg methylprednisolone, 3 mL of 0.5% lidocaine) vs. 32 IL	6 months	> 50% VAS improvement, ODI	TF = IL
Ghahreman et al. 2010 (91) RADIC	150	TF steroids, local anesthetic, saline or intramuscular steroids or saline	12 months Only 24 patients were followed at 6 months or beyond	NRS, RMDQ, SF-36	TF injections provide modest but substantial relief
Tafazal et al. 2009 (92) RADIC/SS	150	TF bupivacaine with or without methylprednisolone	12 months	VAS, ODI	No additional benefit from adding steroids for either pain relief or need for further injections
Jeong et al. 2007 (94) RADIC	239	193 disc herniation; 49 SS Ganglionic (injection of compromised nerve) and pre-ganglionic (injection at level of compromise, one level above compromised nerve)	6 months	>50% VAS improvement	Preganglionic TFESI > ganglionic for short-term and ganglionic > preganglionic for mid-term follow-up
Ackerman and Ahmad 2007 (107) RADIC	90	Series of 3, TF, IL, caudal TF and IL: 4 mL of saline and 1 mL of triamcinolone Caudal 20 mL saline and 1 mL triamcinolone	6 months	Pain relief, ODI, Beck Depression Score	Pain relief more effective with TF

Table 3. *Characteristics of included randomized trials and observational studies. (continued)*

Study/Indications Evaluated (RADIC/ SS/PLLS/LBP)	Number of Patients	Treatment vs. Comparator	Length of Follow-Up	Outcome Parameters	Comments
Bonetti et al. 2005 (96) RADIC/SS	306 166 disc disease 140 stenosis	Intraforaminal O_2-O_3 vs. local anesthetic/steroids	6 months	Modified McNabb method	Oxygen/ozone was effective
Karppinen et al. 2001 (60) RADIC	160	80 (methylprednisolone/ bupivacaine) vs. 80 saline	12 months	Outcomes: (> 75% relief of leg pain)	Both the saline and the local anesthetic/steroid group had relief
Devulder et al. 1999 (100) FBSS	60	Bupivacaine, hyaluronidase, saline vs. bupivacaine, methylprednisolone vs. bupivacaine, hyaluronidase, bupivacaine	6 months	Verbal pain rating score	All 3 injections had relief at 1 month, decreasing at 3 and 6 months. 35% of each group had > 50% relief
Nonrandomized studies					
Ekedahl et al. 2017 (70) RADIC	100	TF, stratified by type of disc herniations, degree of nerve compression	12 months	VAS, ODI	High-grade nerve compression, low age . Short duration of pain or central herniation predicted improvement.
Sariyildiz et al. 2017 (121) RADIC	75	TF betamethasone 40 mg and lidocaine 2%	12 months	50% VAS improvement, ODI, and sleep quality index	73% had >50% pain relief at 12 months
van Helvoirt et al. 2014 (79) RADIC	69	TF with 20 mg dexamethasone and 0.5 mL lidocaine 2%	12 months	Avoidance of surgery, 50% VAS improvement, 50% RMDQ improvement, GPE of at least "satisfaction"	For nonsurgical group (n = 66), good pain relief at 1 year
Manson et al. 2013 (110) RADIC Retrospective case series	91	TF Triamcinolone and 1 mL bupivacaine	6 months +	Avoidance of surgery	TF allowed 56% of patients with disc herniations to avoid surgery
Mendoza-Lattes et al. 2009 (108) RADIC Retrospective case controlled	93	54 TF, 39 caudal Caudal: 2 mL of methylprednisolone or 3 mL of triamcinolone TF: 1.5-2 mL of bupivacaine and methylprednisolone or triamcinolone	12 months	VAS, ODI, SF-36	No difference between caudal and TF
Rosenberg et al. 2002 (117) RADIC	82	82 (60-80 mg) methylprednisolone with 1 mL lidocaine 1.5%, 1 mL bupivacaine 0.25%	12 months	> 50% NRS improvement	TFESI significantly effective in discogenic low back pain and moderately effective in SS
Wang et al. 2002 (119) RADIC Retrospective	69	TF	> 12 months	Avoidance of surgery	77% were able to avoid surgery
Lutz et al. 1998 (118) RADIC	69	69 (9 mg betamethasone and 1.5 mL 2% xylocaine)	6 months	> 50% NRS improvement	TFESI w/steroid effective

Abbreviations: DRG, dorsal root ganglion; FBSS, failed back surgery syndrome; GPE, global perceived effect; IL, interlaminar injection; JOA, Japan Orthopaedic Association; LBP, axial low back pain not of facet or sacroiliac origin; NHRS, National Health Research Systems; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; PLSS, pain after lumbar surgery; RADIC, herniated nucleus pulposus/radicular pain; RMDQ, Roland Morris Disability Questionnaire; SF-36, 36-Item Short Form Survey; SS, spinal stenosis; TF, transforaminal injection; TFESI, transforaminal epidural steroid injection; TNF-α, tumor necrosis factor alpha; VAS, Visual Analog Scale.

Of the 18 RCTs evaluated, 16 evaluated lumbar radicular pain, 4 spinal stenosis, and 1 pain after lumbar surgery. Of these 18 studies, 3 evaluated both radicular pain and spinal stenosis. No RCTs examined transforaminal epidural steroid injections for axial low back pain, not of facet or sacroiliac origin.

Of the nonrandomized trials evaluated, 8 evaluated lumbar radicular pain. No RCTs examined transforaminal epidural steroid injections for spinal stenosis, pain after lumbar surgery, or axial low back pain, not of facet or sacroiliac origin.

As there are more than 5 RCTs for radicular pain and as all the observational studies evaluated only radicular pain, no observational studies were evaluated for any of the indications.

Methodological Quality Assessment

Appendix Table 4, Cochrane review bias analysis, shows the bias analysis of the 19 RCTs considered for review. One study was excluded because of a low Cochrane score (71). Of these 18, 17 had a Cochrane bias score of at least 5 and were included.

Appendix Table 5, the ASIPP IPM–QRB analysis, shows the ASIPP bias and quality analysis for randomized trials. Of the 17 RCTs evaluated, 14 had a score of at least 25 and were included. Three studies were excluded because of a low ASIPP IPM–QRB score (96,107,115).

The ASIPP IPM–QRBNR analysis for nonrandomized studies was not utilized, as no nonrandomized studies were evaluated.

Meta-Analysis

A meta-analysis was performed for radicular pain, with the results presented later.

Study Characteristics

Table 4 shows the study characteristics of the included studies for randomized trials and observational studies evaluating therapeutic lumbar transforaminal injections.

Analysis of Evidence

Evidence is evaluated according to the 4 considered causes of low back pain, radicular pain from disc herniations, from either central or foraminal stenosis, from failed back surgery syndrome, and from axial pain not of facet or sacroiliac origin.

Radicular Pain

Table 5, summary of study results, contains an overview of the pain relief for radicular pain. Our concern here is not the specific question asked by these various studies but whether the studies demonstrate efficacy of transforaminal injections.

A total of 11 RCTs looked at various aspects of transforaminal injections for radicular pain. Most looked at disc herniations, but both Denis et al (75) and Tafazal et al (92) included some patients with foraminal stenosis. The studies were focused on a variety of questions relating to transforaminal injections, including whether

- the critical issue for the success of transforaminal injections is local anesthetic, steroids, or saline solution;
- transforaminal injections are more effective than interlaminar injections;
- parasagittal injections were more effective than transforaminal;
- cytokine inhibitors were effective;
- nonparticulate (solution) steroids were as effective as particulate (suspension) steroids;
- pulsed radiofrequency ablation is effective;
- injection at the level of the disc herniation (preganglionic) is as effective as injections one level below, at the level of the exiting nerve root (ganglionic).

Our focus is on whether transforaminal injections can provide 50% pain relief in patients with radicular pain, rather than the specific questions focused on in the individual studies. Table 5 summarizes the results of the studies.

Of the 11 studies, 9 presented data showing the percent of patients at either 1, 3, or 6 months who had more than 50% relief from transforaminal injections.

Four studies, Ghahreman et al (91), Ghai et al (78), Cohen et al (83), and De et al (67), provided 1-month data, all but Ghahreman finding that regardless of the procedure, all transforaminal patients for radicular pain had at least 50% relief. Ghahreman et al (91) showed that 54% of patients receiving local anesthetics and steroids had relief, whereas only 7% of local anesthetic alone injections were successful and 19% of saline solution alone. These findings were not confirmed by other authors.

Three-month data were provided by Ghai et al (78), Cohen et al (83), Kennedy et al, Denis et al (75), and De et al (67). Again, local anesthetic injections gave roughly 50% relief. Exceptions at 3 months to

Table 4. *Study characteristics of RCTs assessing therapeutic transforaminal epidural injections .*

Study Characteristic Methodological Quality Scoring	Number of Patients and Selection Criteria	Interventions/Control	Outcome Measures	Time of Measurement	Results	Weaknesses	Strengths	Conclusions
Wei et al. 2020 (63) Cochrane 10 IPM–QRB 31 RA, AC	90 patients with mild to moderate one-level central stenosis with unilateral leg pain	TF injections with 2 mL of lidocaine with 10 mg etanercept, 2 mL of lidocaine and 2 mL steroid or 4 mL of lidocaine	VAS, ODI	1, 3, 6 months	Etanercept group had >50% reduction in both mean VAS and ODI at 1, 3, and 6 months. Lidocaine and lidocaine steroid groups did not reach >50% reduction in VAS at any point. The had >40% reduction in ODI at 1 month only. No difference between lidocaine and lidocaine with steroid.	Single blinded study. Method of performing TF injections not described. Mean data only provided; not possible to see how many individuals had significant relief.	Study comparing TNF-α inhibitors transforaminally with LA or LA/starost.	Patients with mild to moderate central stenosis have sustained, significant relief from lidocaine/etanercept injections, but not from LA or LA/steroid injections.
De et al. 2020 (67) RA, DB, AC Cochrane 12 IPM–QRB 35	50 segmental low back pain below the knee for >3 months	All patients who had >75% relief with selective root blocks with 1 mL 2% lidocaine 1 mL of 0.5% bupivacaine at one root; 1 mL of 0.5% bupivacaine with pulsed radiofrequency ablation of the DRG	NRS, ODI	2 weeks, 1, 2, 3, 6 months	>50% reduction of VAS in 100% of pulsed group at 1 month and 96%, 56%, and 20% at 2, 3, and 6 months; For nonpulsed group, results were 56%, 20%, 0%, 0%	Local anesthetic group had only 1 mL injection	Well- controlled study.	Pulsed radiofrequency ablation of the DRG provides long-term relief of lumbar radicular pain.
Makkar et al. 2019 (65) RA, DB, AC Cochrane 12 IPM–QRB 35		65 patients between 20 and 50 years with unilateral radicular pain of >3 months duration, VAS >5/10 Median IL/parasagittal IL/TF 4 mL contrast medium; 80 mg of methylprednisolone and 2 mL of 1% lidocaine, 4 mL total Injections repeated if pain relief <50% or pain returned	>50% in VAS; mean VAS change; MODQ, contrast medium spread; # of ESIs for >50% relief; DEXA scan change at 3 months	2 weeks, 1, 3, 6 months	15/20 TF and 16/20 parasagittal vs. 12/21 IL had >50% relief at 6 months Mean number of ESI = ~2 No change in DEXA scan after injections	Small sample size. Presence of disc herniation not provided.	Well-performed study comparing 3 approaches. Mentions blunt needle techniques, although sharp needles were used.	Both TF and parasagittal IL injections are effective in obtaining >50% pain relief in patients with radicular pain.
Denis et al. 2015 (75) RA, DB, AC Cochrane 12 IPM–QRB 35	56 patients with leg > back pain and concordant imaging	27 = 6 mg betamethasone and 1 mL 2% lidocaine; 7.5 mg dexamethasone and 1 mL 2% lidocaine Injections could be at 1 or 2 levels; injections could be repeated once	VAS, ODI Difference in score; Percentage of patients with >50% improvement in VAS	1, 3, 6 months	~40% of patients required 2 injections. 59% of dexamethasone and 33% had >50% decrease in VAS at 3 months. No statistical difference in VAS between 2 groups at 1, 3, or 6 months	Small sample size; Unclear as to duration of pain or use of conservative treatment. Both disc herniations and foraminal stenosis were evaluated. Study was underpowered.	Precisely performed study.	Both TF dexamethasone and betamethasone are effective in relieving radicular pain. No difference between the 2 according to the primary outcome measure. More dexamethasone patients had >50% relief at 3 months.

Table 4. *Study characteristics of RCTs assessing therapeutic transforaminal epidural injections . (continued)*

Study Characteristic Methodological Quality Scoring	Number of Patients and Selection Criteria	Interventions/Control	Outcome Measures	Time of Measurement	Results	Weaknesses	Strengths	Conclusions
Ghai et al. 2014 (78) RA, DB, AC Cochrane 11 Jason IPM–QRB 39	Unilateral leg pain of >3 months duration not responsive to conservative therapy, pain ≥5 on VAS, with concordant MRI disc herniation	32 parasagittal IL injections and 30 TF 4 mL of contrast medium in both groups. 80 mg of methylprednisolone in normal saline, total volume 4 mL Up to 3 repeat injections allowed	VAS, ODI Primary endpoint >50% reduction in VAS at 3 months	2 weeks, 1, 2, 3, 6, 9, and 12 months	>75% of both groups had >50% relief at 3 months. Pain relief persisted in both groups, with no difference at 12 months. 1.9 procedures per year in each group Perineural spread was the same in both groups; TF had more ventral spread.	Unclear as to which cointerventions were provided to which patient; No local anesthetic used.	Well-designed and implemented study. Fully powered.	Repeated TF and parasagittal IL injections are effective in providing pain relief and increased function in patients with discogenic radicular pain.
Kennedy et al. 2014 (81) RA, DB, AC Cochrane 11 IPM–QRB 33	Unilateral radicular pain of <6 months duration and VAS ≥4/10 and single level disc protrusion	41 = solution (dexamethasone) 37 = suspension (triamcinolone) Single-level, unilateral TF 1 mL contrast medium then 2 mL 2% lidocaine followed by 1.5 mL dexamethasone (15 mg) or 1.5 mL triamcinolone (60 mg) Up to 3 injections or referral to surgery allowed	Need for surgery; number of injections; % of patients getting >50% relief; ODI	2–3 weeks, 3 months, 6 months	>70% of both groups had ≥50% relief at 3 and 6 months. Both groups went from severe disability to minimal disability on ODI. Average number of injections ~1.5. 17% of dexamethasone had 3 injections vs. 2.7 of triamcinolone >50% of patients had only one injection	Underpowered study.	Well-designed and implemented study.	Both solution and suspension steroids delivered transforaminally are effective in treating radicular pain from a disc herniation.
Manchikanti et al. 2014 (77) RA, DB, AC Cochrane 12 IPM–QRB 44	Disc herniation at L4-5 or L5-S1 with unilateral radiculitis of at least 6-months duration, not responsive to conservative treatment	TF 60 = 1.5 mL 1% lidocaine and 0.5 mL saline 60 = 1.5 mL 1% and 0.5 mL betamethasone (3 mg) Repeat injections allowed	>50% improvement in pain relief and functional status	3, 6, 12, 18, and 24 months	NRS, ODI At 6 months, 73% of all patients in the local anesthetic group and 67% in the steroid group had >50 improvement in VAS and ODI. At 2 years, the result was 65% and 57%. ~3.5 injections/year ~12 weeks relief per injection	Lidocaine group had a higher BMI than the steroid group.	Well-designed and implemented study.	Repeat TF with either lidocaine alone or lidocaine and betamethasone are effective in providing improved pain and function in patients with radicular pain from disc herniations.
Cohen et al. 2012 (83) RA, DB, AC Cochrane 12 IPM–QRB 37	8–70 years of age with lumbosacral radiculopathy from 1–6 months in duration with concordant disc pathology on MRI	TF 28 = 60 mg prednisolone and saline 2 mL/0.5 mL 0.5% bupivacaine 26 = 4 mg etanercept in 2 mL water/5 mL 0.5% bupivacaine 30 = 2 mL saline/0.5 mL 0.5% bupivacaine If 2 levels, the dose was divided between each level Injection could be repeated x1 in 2 weeks	NRS, ODI, analgesic use, GPE >50% reduction in VAS and positive GPE Primary outcome average pain for 1 week prior to the 1-month visit	1, 3, and 6 months 3- and 6-month visit only in patients who had >50% reduction in pain and positive GPE	At 1 month, >50% relief and positive GPE in 80% of steroid group; 50% in etanercept and saline groups. At 6 months, >50% relief and positive GPE in 29% of steroid group; 38% in etanercept group and 43% of saline group. No significant difference between groups at 1 month.	Saline is an active treatment, not a placebo. Average duration of pain. Significant proportion of enrollees were young, male servicemen. Other than one repeat injection at 2 weeks, repeat injections were not allowed.	Well-designed and implemented study.	LA combined with either saline, steroid, or etanercept are effective in reducing leg pain from disc pathology.

Table 4. *Study characteristics of RCTs assessing therapeutic transforaminal epidural injections . (continued)*

Study Characteristic Methodological Quality Scoring	Number of Patients and Selection Criteria	Interventions/Control	Outcome Measures	Time of Measurement	Results	Weaknesses	Strengths	Conclusions
Rados et al. 2011 (88) RA, DB, AC Cochrane 11 IPM–QRB 35	Chronic unilateral radicular pain caused by an MRI documented disc herniation or positive EMG All disc pathology was at L4-5 or L5-S1	32 = TF 3 mL 0.5% lidocaine/ 40 mg methylprednisolone 32 = IL 8 mL 0.5% lidocaine/80 mg methylprednisolone All enrollees had 3 injections spaced 2 weeks	VAS, ODI, GPE	3, 6 months	Average VAS at 6 months for IL went from 7.36 to 4.0; for TF, average VAS went from 6.72 to 3.8. Average ODI at 6 months for IL went from 52% to 39%; for TF, average ODI went from 53% to 38%.	Percentage of patients getting >50% relief not provided or extractable from information provided. Treatments not comparable between groups.	High-quality study.	Study failed to show that a single series of 3 IL or TF injections provide >50% relief.
Ghahreman et al. 2010 (91) RA, DB, True Placebo Control Cochrane 11 IPM–QRB 33	Adults with radicular, lancinating, pain with positive straight leg raising and confirmation disc pathology on CT or MRI and who were believed to be surgical candidates Foraminal stenosis was exclusionary Pain <3 months was acute; chronic if >3 months	TF: 28 = 0.75 mL 0.5% bupivacaine/1.75 mg (70 mg) triamcinolone 27 = 2 mL 0.5% bupivacaine 37 = 2 mL normal saline Intramuscular: 28 = 1.75 mL (70 mg) triamcinolone 30 = 2 mL normal saline Up to 3 injections were allowed	NRS, RMDQ, SF36, Patient-Specified Functional Outcomes Scale Primary outcome >50% relief at 1 month	1, 3, 6, 12 months	TF: Steroids: 15 of 28 had >50% relief at 1 month LA: 2 of 27 had >50% relief at 1 month Saline: 7 of 37 had >50% relief at 1 month IM: Steroids: 6 of 28 had >50% relief at 1 month Saline: 4 of 30 had >50% relief at 1 month At 6 months, 9 of TF steroid, 3 TF saline, 1 TF LA, 6 of the IM steroid and 4 of the IM saline had >50% relief.	Study was underpowered. TF steroid response was bimodal. TF saline response had a large standard deviation.	Only true placebo study reviewed.	TF steroids and TF saline are more effective than TF LA or IM injections. Greater response from placebo than TF LA. TF steroids with the option of a second injection is a viable alternative to surgery for lumbar radicular pain owing to disc herniation.
Tafazal et al. 2009 (92) RA, DB, AC Cochrane 11 IPM–QRB 27	Unilateral leg pain with concordant MRI disc herniation or foraminal stenosis, failed 6 weeks of conservative therapy	TF 76 = 2 mL of 0.25% bupivacaine 74 = 2 mL of 0.25% bupivacaine/40 mg methylprednisolone One enrollee had a repeat injection	VAS, ODI, Low Back Outcome Score 2-point change in VAS or 10% change in ODI	6 weeks, 3 months, 12 months	Mean change in VAS at 3 months was ~23% for both groups. ODI change ~10%. No difference between disc herniation and foraminal stenosis. Disc prolapse had ~13% improvement in ODI vs. ~5% for stenosis.	Endpoints were only 2-point change in VAS or 10% ODI.	High enrollment.	Steroids did not offer any additional benefit over LA. Neither group had >50% relief. Disc prolapse did same as foraminal stenosis.
Jeong et al. 2007 (94) DB, AC Cochrane 9 IPM–QRB 28	Lumbosacral radiculopathy or root compression on imaging or central stenosis	TF 127 = at level of exiting nerve root (ganglionic) or 112 = at level of compression (preganglionic or one level above ganglionic) 0.5 mL 0.5% bupivacaine/40 mg triamcinolone	VAS 4-point scale of subjective improvement >50% improvement of VAS	1 and 6 months	88% of preganglionic had >50% relief at 1 month; 71% of ganglionic did. At 6 months, it was 69% and 60.4% No difference between central stenosis and disc herniation	Randomization and cointerventions not clear.	Large enrollment.	Both ganglionic and preganglionic injections are effective, preganglionic more so.

Table 4. *Study characteristics of RCTs assessing therapeutic transforaminal epidural injections . (continued)*

Study Characteristic Methodological Quality Scoring	Number of Patients and Selection Criteria	Interventions/Control	Outcome Measures	Time of Measurement	Results	Weaknesses	Strengths	Conclusions
Karppinen et al. 2001 (60) RA, DB, AC Cochrane 12 IPM–QRB 34	Back and unilateral leg pain of 3–28 weeks duration	TF L4, L5, or S1 79 = methylprednisolone/ bupivacaine 79 = saline	VAS, straight leg raise	2 weeks, 1, 3, 6, 12 months	At 6 months, mean pain reduction was 56% in LA/steroid group and 71% in saline group.	No description of MRI findings. AC.	Large, well-designed study.	Both LA/steroid and saline alone are effective in reducing radicular pain.
Devulder et al. 1999 (100) RA Cochrane 8 IPM–QRB 27	Discectomy patients with EMG documented pathology involving 1 or 2 roots and fibrosis on MRI or epidurogram	TF 20 = 1 mL bupivacaine 0.5%/1500 U hyaluronidase/1 mL saline 20 = 1 mL bupivacaine 0.5%/40 mg methylprednisolone 20 = 1 mL bupivacaine 0.5%/1400 U hyaluronidase/40 mg methylprednisolone	Verbal pain rating scale	1, 3, 6 months	At 3 months, 30% of patients in all groups had >50% relief. At 6 months, 27% of patients in all groups had >50% relief.	Underpowered study. Moderate quality.	Only study looking at post lumbar surgery syndrome.	TF injections with LA with or without steroids or hyaluronidase can relieve leg pain.

Abbreviations: AC, active control; BMI, body mass index; CT, computed tomography; DB, double-blind; DEXA, dual energy x-ray absorptiometry; DRG, dorsal root ganglion; EMG, electromyography; ESI, epidural steroid injection; GPE, global perceived effect; LA, local anesthetic; IL, interlaminar injection; IM, intramuscular; MODQ, Modified Oswestry Disability Questionnaire; MRI, magnetic resonance imaging; NRS, Numeric Rating Scale; ODI, Oswestry Disability Index; RA, randomized; RMDQ, Roland Morris Disability Questionnaire; TF, transforaminal injection; SF-36, 36-Item Short Form Survey; TNF-α, tumor necrosis factor alpha; VAS, Visual Analog Scale.

this were the Cohen et al findings for saline solution and etanercept in which approximately 42% of patients had success, Denis et al (75) in which only 33% of patients receiving particulate steroids had success, and De et al (67) who reported that no patients had 50% relief.

Six-month data were provided by 9 authors with more than 50% relief from all but Ghahreman et al (91), Cohen et al (83), and De et al (67).

Thus applying ASIPP's Grading of Evidence criteria, there is a Level I evidence supporting the use of transforaminal epidural injections, with or without steroids, for radicular pain arising from disc herniation.

Meta-Analysis for Radicular Pain

Single-arm meta-analysis was performed for pain relief and functionality improvement in patients with radicular pain utilizing data from 9 studies (60,65,75,77,78,81,88,92,115).

Figure 1A shows changes from baseline at 3 months in patients with radicular pain treated with methylprednisolone acetate with a 3.72-point decrease on 0 to 10 cm Visual Analog Scale (VAS). Figure 1B shows changes from baseline at 3 months in patients treated with other particulate steroids (betamethasone and triamcinolone) with 4.13-point decrease in radicular pain. Figure 1C shows 4.29-point decrease in radicular pain in patients treated with dexamethasone (nonparticulate steroid). All differences were highly statistically significant ($P < 0.001$).

Figure 2A shows changes in functionality from baseline at 3 months in patients with radicular pain treated with methylprednisolone acetate with 20.61-point decrease on 0 to 100 Oswestry Disability Index (ODI) scale. Figure 2B shows changes from baseline at 3 months in patients treated with other particulate steroids (betamethasone and triamcinolone) with 22.48-point improvement in functionality. Figure 2C shows 28.52-point functionality improvement in patients treated with dexamethasone (nonparticulate steroid). All differences were highly statistically significant ($P < 0.001$).

Figure 3A shows changes from baseline at 6 months in patients with radicular pain treated with methylprednisolone acetate with 4.24-point decrease on 0 to 10 cm VAS. Figure 3B shows changes from baseline at 6 months in patients

Table 5. *Summary of study results, radicular pain.*

Radicular Pain			% Patients with ≥ 50% Relief from TF		
Study Goal	**Study Question**	**Findings**	**1 month**	**3 months**	**6 months**
Role of injectate					
Manchikanti et al. 2014 (77)	Compare TF LA injections with and without steroids.	TF without or with steroids are effective.			LA alone 73% steroid 67%
Ghahreman et al. 2010 (91)	Compare TF LA, LA/steroid, saline and IM, steroid and saline.	TF injections are superior, decreasing over time.	TF: LA/steroids 54% LA 7% saline 19% IM steroid 21% saline 13%		TF: LA/steroids 32% LA 4% saline 11% IM steroid 21% saline 13%
Tafazal et al. 2009 (92)	Are LA/steroids effective vs. LA alone effective in disc herniations or foraminal stenosis?	Steroids did not provide any additional benefit. HNP group had approximately 25/100 reduction in VAS.		NA	NA
Karppinen et al. 2001 (60)	Are steroids effective in TF injections?	Both LA/steroid and saline groups had mean reduction of ≥ 50% at 3 and 6 months.		NA	NA
TF vs. IL					
Rados et al. 2011 (88)	Compare TF vs. IL injections.	Both approaches are effective.			TF 50% IL 53%
TF vs. parasagittal					
Makkar et al. 2019 (65)	Compare TF vs. midline IL vs. parasagittal IL.	TF and PIL more effective than IL. Number of injections same in each group.			80% TF; 75% PIL 57% MIL
Ghai et al. 2014 (78)	Compare TF vs. parasagittal.	Both routes effective.	63%	76.7%	76.7%
Cytokine inhibitors					
Cohen et al. 2012 (83)	Are steroids, etanercept, or saline more effective?	No statistical difference between the groups.	75% steroid; 50% saline; 42% etanercept	50% steroid; 43% saline; 42% etanercept	29% steroid; 40% saline; 38% etanercept
Particulate vs. nonparticulate					
Kennedy et al. 2014 (81)	Are particulate and nonparticulate steroids equally effective?	Both are effective. Fewer injections with particulate.		>70% of both groups	>70% of both groups
Denis et al. 2015 (75)	Are particulate and nonparticulate steroids equally effective? ~75% of patients had disc herniations.	No statistical difference between the particulate and nonparticulate groups.		59% nonparticulate 33% particulate	
Pulsed radiofrequency					
De et al. 2020 (67)	Is pulsed radiofrequency ablation of the DRG as effective as LA/steroid?	Longer term relief from a single pulsed radiofrequency procedure than a single LA/steroid.	100% pulsed radiofrequency; 56% LA/steroid	72% pulsed radiofrequency; 0% LA/steroid	28% pulsed radiofrequency; 0% LA/steroid
Level of injection					
Jeong et al. 2007 (94)	Compare effectiveness of differing injection levels. 80% of patients had disc herniations.	Both approaches are effective.	71% ganglionic; 88% preganglionic		67% ganglionic; 60% preganglionic

Abbreviations: DRG, dorsal root ganglion; HNP, herniated nucleus pulposus; IM, intramuscular; IL, interlaminar epidural injection; LA, local anesthetic; MIL, midline interlaminar injection; NA, not available; PIL , parasagittal interlaminar injection; TF, transforaminal epidural injection.

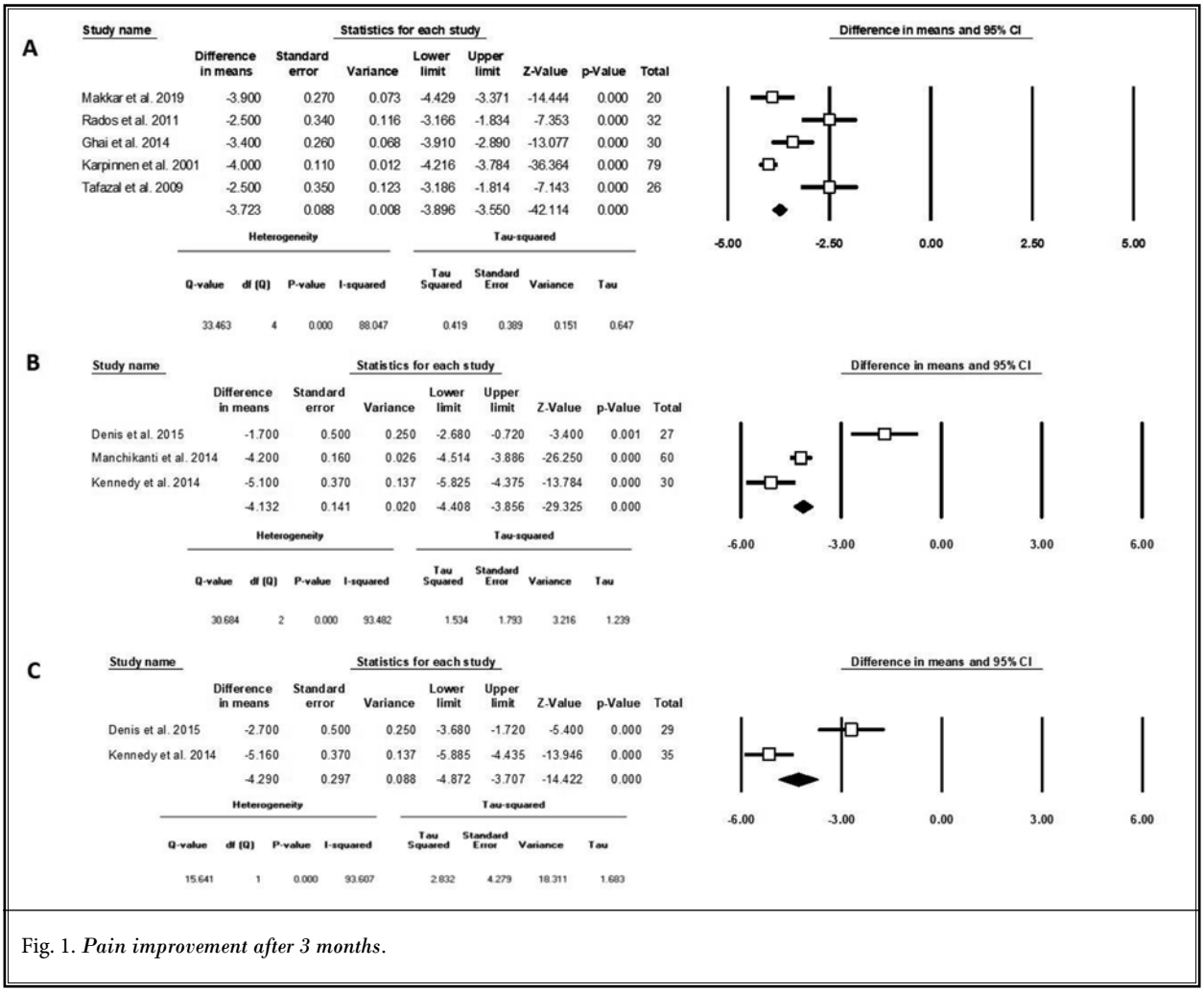

Fig. 1. *Pain improvement after 3 months.*

treated with other particulate steroids (betamethasone and triamcinolone) with 4.41-point decrease in radicular pain. Figure 3C shows 5.29-point decrease in radicular pain in patients treated with dexamethasone (nonparticulate steroid). All differences were highly statistically significant ($P < 0.001$).

Figure 4A shows changes in functionality from baseline at 6 months in patients with radicular pain treated with methylprednisolone acetate with 28.79-point decrease on 0 to 100 ODI scale. Figure 4B shows changes from baseline at 6 months in patients treated with other particulate steroids (betamethasone and triamcinolone) with 21.27-point improvement in functionality. Figure 4C shows 31.86-point functionality improvement in patients treated with dexamethasone (nonparticulate steroid). All differences were highly statistically significant ($P < 0.001$).

Pain from Spinal Stenosis

Central Stenosis

Two studies looked at central stenosis: Wei et al (63) and Jeong et al (94). Wei et al (63) examined the effectiveness of a TNF-α inhibitor, etanercept, with local anesthetic versus local anesthetics alone versus local anesthetics and steroids in patient with single-level mild to moderate central stenosis. Wei et al (63) found that although there was no significant statistical difference between the 3 groups, only the etanercept group had a mean greater than 50% relief at 1, 3, and 6 months. The report did not indicate what percent of patients had greater than 50% relief. Jeong et al (94) looked at both disc herniations and central stenosis, with 20% of the patients having central stenosis. The study did not break out results by diagnosis, so that it

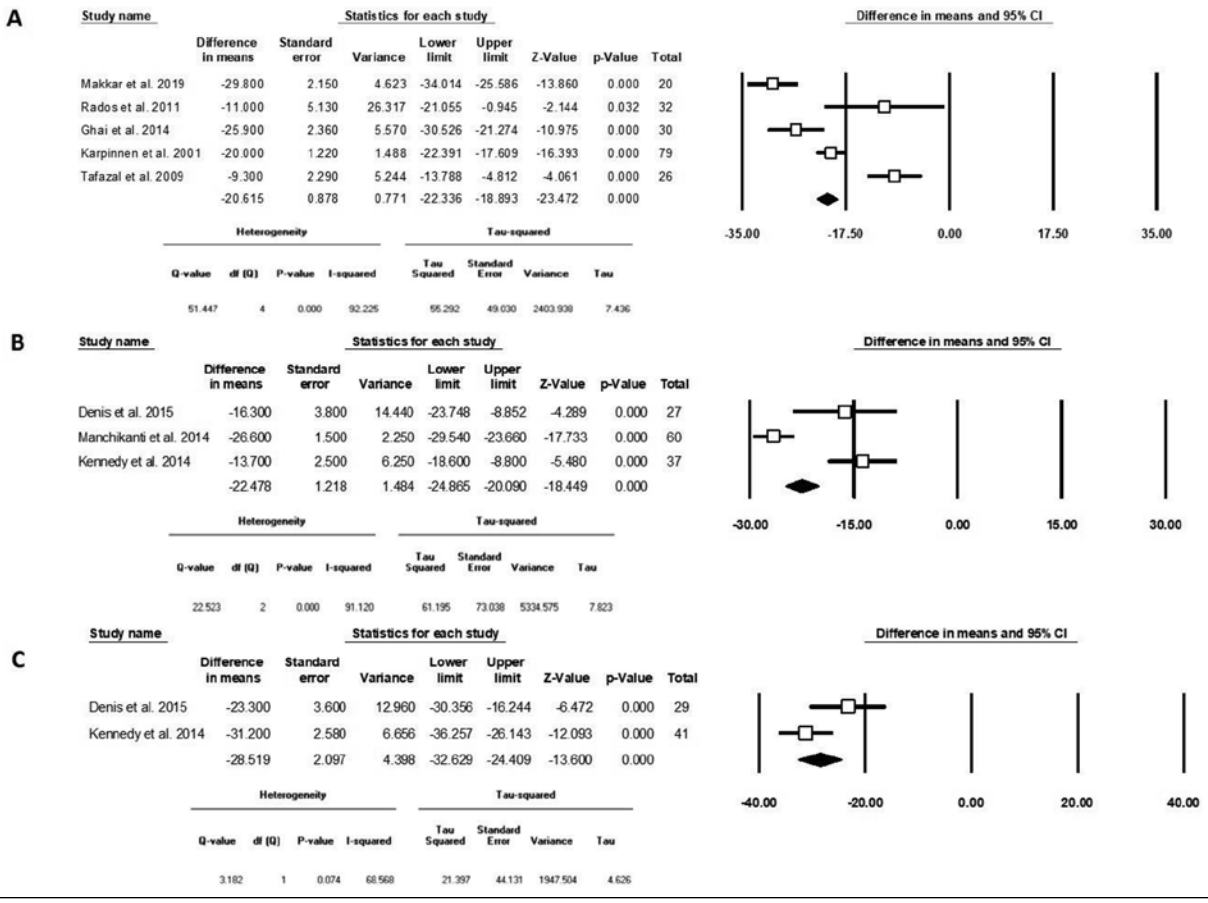

Fig. 2. *Functionality improvement after 3 months.*

is not possible to assess the effectiveness of transforaminal injections in central stenosis from the Jeong et al (94) study.

As the Wei et al (63) study is of moderate quality, so that there is one moderate quality RCT and no observational studies supporting the role of transforaminal injections for central stenosis, the ASIPP level of evidence is IV (Table 6).

Foraminal Stenosis

Tafazal et al (92) specifically looked at whether there was any difference in the efficacy of transforaminal injections with local anesthetic versus local anesthetic and steroid depending on whether the cause of the radicular pain was foraminal stenosis versus disc herniation. In addition to the article's generalized conclusion that steroids did not offer additional benefit, when looking specifically at the foraminal stenosis subset, that there was a trend toward better outcomes from disc herniations than from foraminal stenosis. However, none of the groups met the current criteria of 50% relief.

In the Denis et al (75) 2015 study, approximately 25% of the patients had foraminal stenosis. The study did not break out results by underlying pathology, disc herniation, or foraminal stenosis, so that it is not possible to determine the efficacy of transforaminal injections for foraminal stenosis based on this article.

Applying ASIPP's grading criteria, any recommendation regarding the use of transforaminal epidural steroid injections for radicular pain caused by foraminal stenosis would have to be Level V, Consensus (Table 7).

Pain after Lumbar Surgery

One study, the Devulder et al (100) moderate quality 1999 article, looked specifically at the efficacy of

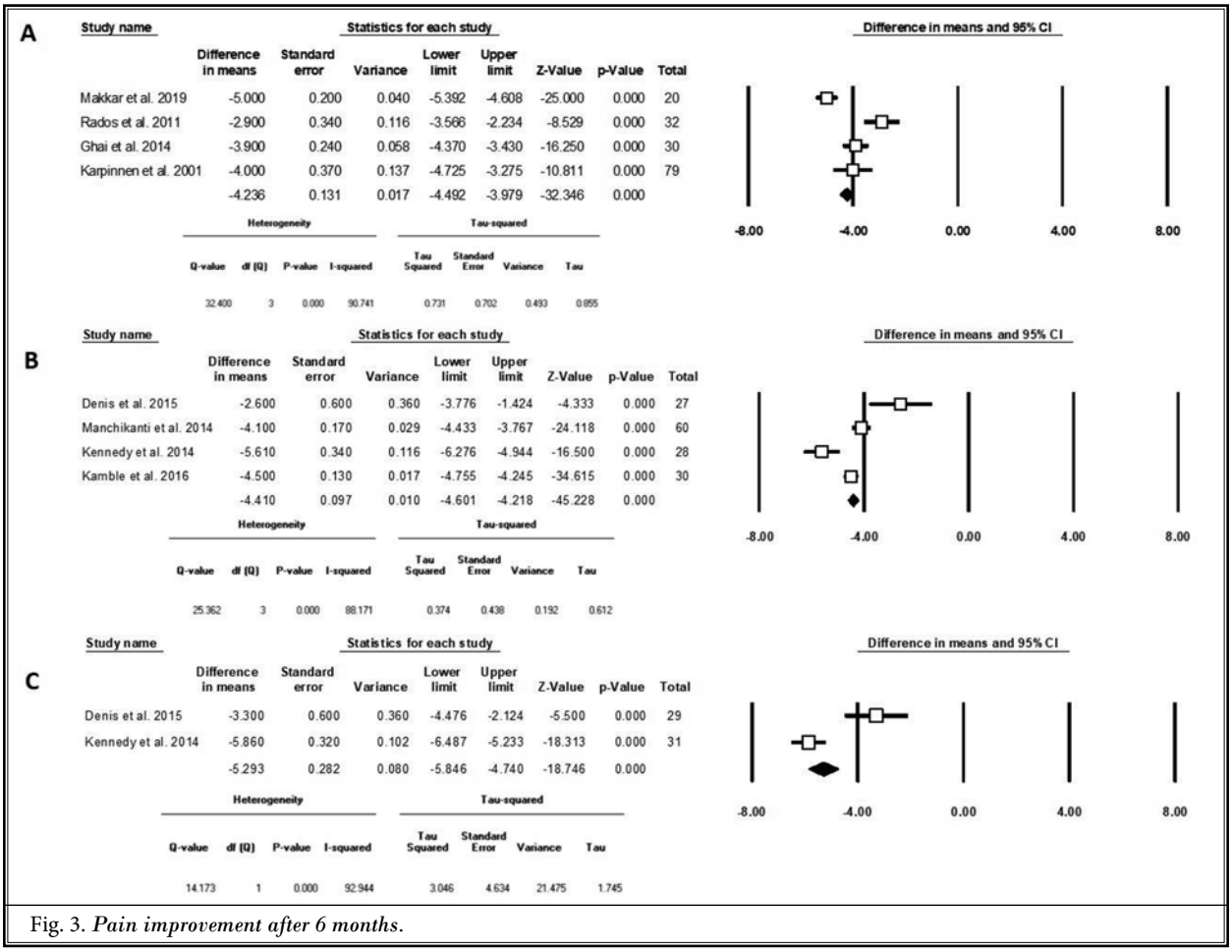

Fig. 3. *Pain improvement after 6 months.*

Table 6. *Summary of study results, pain from central stenosis.*

Pain from Central Stenosis			% Patients with ≥ 50% Relief from TF		
Study Goal	**Study Question**	**Findings**	**1 month**	**3 months**	**6 months**
Relief from radicular pain from central stenosis					
Wei et al. 2020 (63)	Are LA/etanercept, LA, and LA/steroid equally effective?	Only the etanercept group had > 50% mean decrease in VAS at 1, 3, and 6 months.	NA	NA	NA
Jeong et al. 2007 (94)	Compare effectiveness of differing injection levels. 20% of patients had disc herniations.	Both approaches are effective.	71% ganglionic; 88% preganglionic		67% ganglionic; 60% preganglionic

Abbreviations: LA, local anesthetic; NA, not available; TF, transforaminal epidural injection.

transforaminal injections for pain after lumbar surgery, specifically that caused by epidural fibrosis. This study compared the efficacy of local anesthetic and hyaluronidase, local anesthetic and steroid, and local anesthetic with both hyaluronidase and steroid.

Devulder et al (100) found that all 3 injectates provided significant relief at 3 and 6 months for 30% of patients.

Based on ASIPP criteria, with one moderate quality RCT, there is Level IV evidence supporting the use of transforaminal injections for post lumbar surgery syndrome (Table 8).

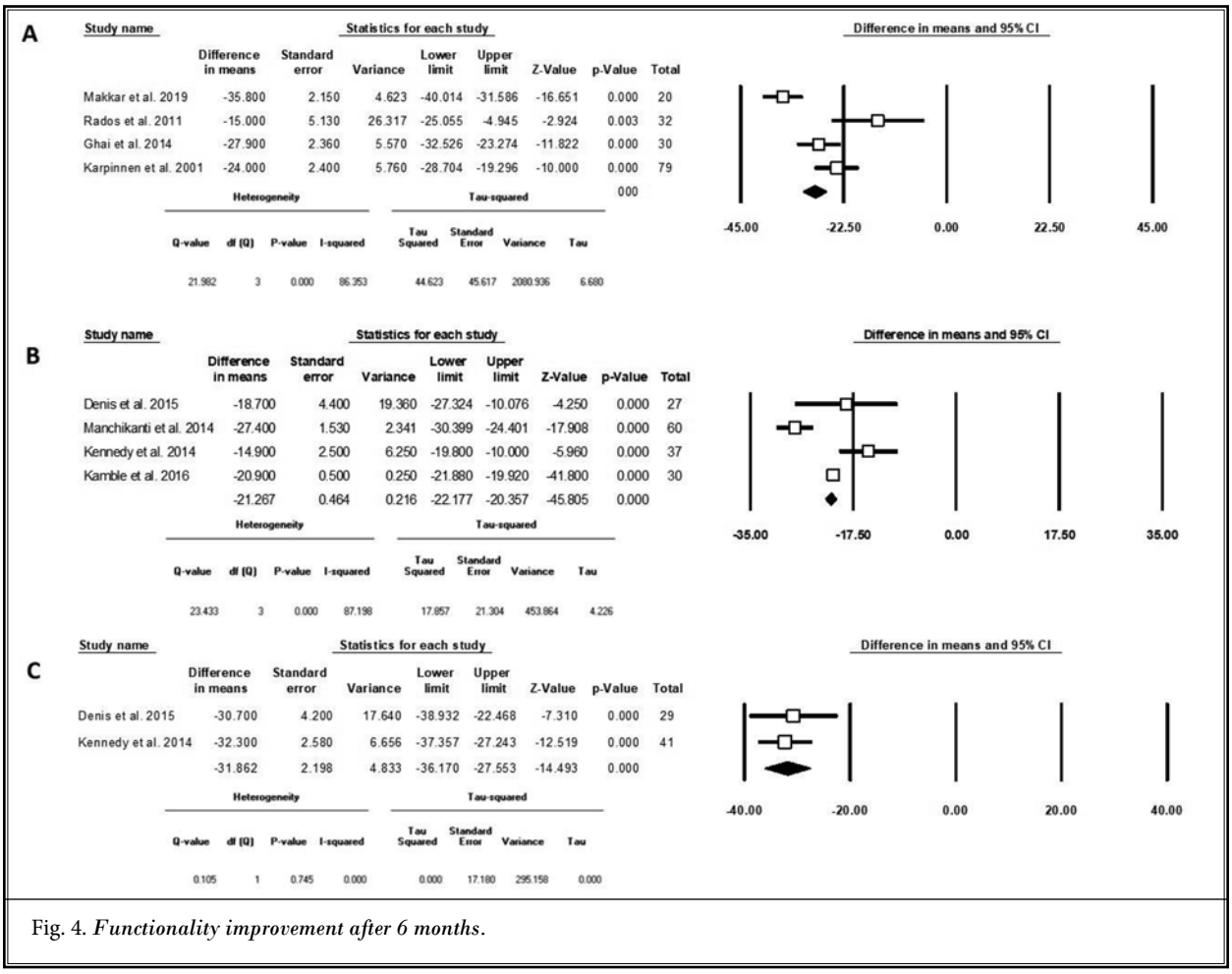

Fig. 4. *Functionality improvement after 6 months.*

Table 7. *Summary of study results, pain from foraminal stenosis.*

Foraminal Stenosis			% Patients with ≥ 50% Relief from TF		
Study Goal	**Study Question**	**Findings**	**1 month**	**3 months**	**6 months**
Relief from radicular pain from foraminal stenosis					
Tafazal et al. 2009 (92)	Are LA/steroids vs. LA alone effective in disc herniations or foraminal stenosis? Approximately one-third of patients had foraminal stenosis .	Steroids did not provide any additional benefit. Stenosis group had approximately 20/100 reduction in VAS.		NA	NA
Denis et al. 2015 (75)	Are particulate and nonparticulate steroids equally effective? ~25% of patients had foraminal stenosis.	No statistical difference between the particulate and nonparticulate groups.		59% nonparticulate 33% particulate	

Abbreviations: LA, local anesthetic; NA, not available; TF, transforaminal epidural injection.

Table 8. *Summary of study results, pain after lumbar surgery.*

Pain after Lumbar Surgery		% Patients with ≥50% Relief from TF			
Study Goal	**Study Question**	**Findings**	**1 month**	**3 months**	**6 months**
Relief from radicular pain after lumbar surgery					
Devulder et al. 1999 (100)	Is there any difference between the efficacy of local anesthetics with hyaluronidase, local anesthetics with steroids, or local anesthetics with hyaluronidase and steroids?			30%	27%

Abbreviations: TF, transforaminal epidural injection.

Axial Low Back Pain Not of Facet or Sacroiliac Origin

No studies evaluated the role of transforaminal injections for axial low back pain. Accordingly, any recommendations relating to transforaminal injections for axial low back pain would be ASIPP Level V, Consensus.

Complications

The RCTs reviewed indicate that transforaminal injections are generally safe. Most of the studies reported no complications (63,91,92,94). Of those that did report complications, the most common was increased pain after the injection, which resolved spontaneously without the need for treatment (83). Denis et al (75) also reported only transient complications, although one patient had a dural puncture requiring an epidural blood patch.

Despite this apparently benign profile, the FDA Adverse Event Reporting System received 90 reports of serious complications after epidural injections, including all injection approaches and spinal locations, between 1997 and 2014 (127). In 2014, the FDA mandated that a class warning be added to all injectable steroids stating that serious neurologic events had been reported after epidural injections (128). The FDA held an advisory committee meeting in November 2014, the result of which was that the FDA did not change the class warning (129).

There are specific concerns regarding transforaminal epidural steroid injections, with multiple reports of cord infarct (130-137). Much of the focus on the cause of the neurologic catastrophes has been on the role of particulate steroids in embolizing the cord (138-140). That concern is seen in this systematic review, with the number of studies comparing the effectiveness of particulate and nonparticulate steroids and with the FDA's report that the use of nonparticulate steroids for lumbar transforaminal epidural steroid injections increased from 5% of non-Medicare injections to 15% between 2009 until 2013 (127).

The role of particulate steroids in causing infarct is called into question by the Gharibo et al (141) report of conus medullaris infarct after a transforaminal injection of dexamethasone. Further casting doubt on the role of emboli as the cause of lumbar transforaminal neurologic catastrophes is the experiment of nature of atheromatous emboli. Slavin et al (142), in a postmortem study, found that atheromatous embolization of the lumbosacral cord was common in patients with abdominal aortic grafts or with atheromatous emboli to other viscera. However, the lumbosacral emboli were generally subclinical and involved the arteries of the distal cord, where the anterior spinal artery bifurcates and joins the posterior spinal arteries. The relatively benign nature of atheromatous lumbar emboli stands in contrast to their causative role in cervical or cerebral infarcts.

Shah (143) has evaluated the possible mechanisms of infarct of the artery of Adamkiewicz, concluding that embolization is unlikely, with more likely causes being intimal flap or vasospasm rather than intraarterial injection of particulate steroids. The goal of a safe transforaminal steroid injection should be to avoid the artery.

The traditional approach to transforaminal injections has been a supraradicular technique, in which the needle placed above the nerve root. Murthy et al (144) and Kroszczynski (1) independently documented that the artery of Adamkiewicz is located in the superior one-half of the foramen 97% of the time. Glaser and Shah (145), Atluri et al (146), and Jasper (147) have recommended an infraradicular, or the Kambin triangle (148), approach to avoid the radiculomedullary artery.

The use of blunt needles is another approach to avoiding damage to the artery: if the wall of the artery cannot be punctured, then one will not cause radiculomedullary intraluminal injection, intimal flap, or vasospasm. One would also not be able to impinge on a medullary artery or to cause intraneural retrograde injection.

Intraneural injections can also cause neurologic compromise by pressure ischemia of the fascicles or retrograde flow (149). Although one would expect that because lumbar injections are done at the level of the cauda equina, one would expect that damage from intraneural injections would be limited to the nerve root injected, Selander and Sjöstrand (150) showed that endoneurial injections into the rabbit sciatic nerve could reach the cord.

Scanlon et al (151) has suggested the use of blunt needles for cervical injections. Heavner et al (152) has shown that blunt needles cannot puncture arteries or nerves, thus removing the risk of neural damage. Ozcan et al (153) found significantly few vascular penetrations with blunt tip needles than with sharp needles, but failed to distinguish between venous and arterial penetration. One would not expect blunt needles to protect against intravenous injections; the complications of concern come from arterial or intraneural impingement. Smuck et al (154) also looked at occurrence of inadvertent intravascular injections with blunt-tip, pencil-point, and catheter-extension needles, finding comparable rates of intravascular injection with blunt-tip and pencil-point needles. The Smuck et al (154) study was characterized by a failure to distinguish between venous and arterial injections.

Akins et al (155) developed a blunt needle to intraabdominal drainage procedures and found that blunt needles would not damage the arteries. Kim et al (156) performed a systematic review of needle type and intravascular injection, finding that both blunt needles and pencil-type needles had a lower risk of intravascular injection.

In discussing blunt needles, it is important to note that pencil-tip needles, such as Sprotte or Whitacre, have punctured arteries in patients (157). There are no such reports with blunt-tip needles.

A blunt needle should systematically change how transforaminal injections are performed to remove the risk of cord infarct.

Van Boxem et al (158) have recently published a comprehensive review of the safety of epidural steroid injections, examining all levels of the spine and all epidural approaches. The recommendations of the work group supported an infraneural approach, but looking at the occurrence of venous injections, did not recommend the use of blunt needles.

Discussion

Epidural injections were initially performed via the caudal approach with local anesthetics. The interlaminar approach was soon added, followed later by the addition of steroids. In the late 1990s, the transforaminal approach was developed as a means of getting medication directly to the presumed site of pathology (118,159).

Transforaminal injections have been the source of discussion regarding multiple issues, including safety, efficacy, technique, and policy issues related to changes in which approach to the epidural space physicians have been utilizing.

This review has shown Level I evidence, multiple high-quality RCTs, supporting the use of transforaminal epidural for radicular pain caused by disc herniations.

A meta-analysis shows highly significant improvements in pain and function with both particulate and nonparticulate steroids for radicular pain.

For both radicular pain from central stenosis and from post lumbar surgery syndrome, each indication has one moderate quality RCT, with Level IV evidence supporting the use of transforaminal epidural injections in these 2 settings.

For foraminal stenosis and for discogenic axial pain, the level of evidence is Level V, Consensus.

Absence of evidence is not evidence of absence. Care provided to any individual patient demands the integration of analysis of the evidence, the physician's clinical expertise, and patient preference (160).

Several other issues need to be addressed when evaluating transforaminal injections.

What to Inject Transforaminally

The reviewed studies demonstrated a rich interest in the various injectates. Manchikanti et al (77) showed repeated transforaminal injections with local anesthetic were as effective as local anesthetic and steroids. Ghahreman et al (91), who also allowed repeated injections, found greater benefit when steroids were included, but to a lesser extent. Tafazal et al (92) and Karppinen et al (60), both of whom provided one injection, found no additional benefit from steroids.

Cohen et al (83), providing 2 transforaminal injections, found no difference between a TNF-α inhibitor,

steroid, and saline solution. Wei et al (63), with one injection, found no difference between a TNF-α inhibitor, steroid, or local anesthetic.

Thus it is up to the individual physician's preference what to inject: transforaminal epidural steroid injections can be done without steroids. The optimal injectate has not been determined. The role of agents such as TNF-α inhibitors remains open.

Role of Pulsed Radiofrequency

De et al (67) found that pulsed radiofrequency of the dorsal root ganglion (DRG) coupled with local anesthetic was more effective than a local anesthetic/steroid injection. Although requiring replication of results and clarity as to the role of the pulsed radiofrequency versus the local anesthetic, the De et al (67) research does point the way for further investigation.

Number of Injections

Only one study, published in 2007, provided a "series of 3" injections, confirming that the "series of 3" is no longer an accepted practice (107). Individual protocols in the studies varied, but a general theme was to allow repeat injections at a minimum of a 2-week interval, with no specific maximum number of injections defined. ASIPP Guidelines (28) recommend a diagnostic phase of up to 2 procedures separated by at least 2 weeks. If these injections provide at least 50% relief for 8 weeks, then repeat injections can be provided at a minimum of 8-week intervals, with a maximum of 4 injections per year.

Location of Injection

Makkar et al (65) and Ghai et al (78) compared transforaminal versus parasagittal interlaminar injections, finding no difference between the efficacy of the 2 approaches.

A supraradicular, "safe triangle" approach was the initial approach recommended for transforaminal injections (161). With the documentation of neurologic catastrophes associated with this approach, Glaser and Shah (145) has recommended a infraneural approach to avoid the radiculomedullary artery.

Lee et al (95) and Kim et al (123), in separate studies not included in this analysis because of short-term follow-up, found no difference between a supraradicular and infraneural approach. The approach used in this study was in a region of the foramen where the radiculomedullary has been found. Bosscher et al (162) documented an innervated peridural membrane located in the infraneural space as a potential source of pain. In that infraneural injections may obliterate this membrane and in that this approach avoids the artery, an infraneural approach seems attractive.

Particulate Versus Nonparticulate

Both particulate and nonparticulate steroid preparations are effective in treating radicular pain. The position that nonparticulate steroids are safer are difficult to sustain in view of the Gharibo et al (141) report of a cord infarct with an L4 transforaminal injection with dexamethasone.

Both particulate and nonparticulate steroids are used off label. FDA approval of a steroid preparation for epidural use would strongly tilt the discussion toward the use of the on-label preparation.

Needle Type

Concern about needles is driven by concern about damage to the artery. Although there is sound evidence that, in the lumbar region, the issue is not intraarterial injection of particulates, concern over issues such as the creation of an occlusive intimal flap is paramount. Studies comparing in vivo use of various needle types have been confounded by failure to distinguish between critical arterial injections and noncritical venous injections. Two studies have directly looked at intraarterial injections, both finding that blunt (not pencil-tip) needles cannot enter the artery. Based on these 2 studies, only blunt needles remove the risk of neural catastrophe from transforaminal injections.

Regardless of needle type, controlled placement of the needle, to prevent either neural or vascular impingement or intradiscal placement, is important. The use of a direction, depth, direction approach is recommended. The needle direction is first obtained fluoroscopically. The angle of the fluoroscope is then changed to monitor the needle's ventral advancement until it is close to, but not at, the target level. The fluoroscope is then returned to the original position for the final advancement to ensure that the needle tip is in the correct position on that view.

Volume of Injections

The effect of volume on injections has had limited study. The Rabinovitch et al (163) study on the effect of epidural volume did not provide any data regarding epidural injections.

Kim et al (123) used high-volume injections, 9 mL total, to look at spreading patterns and pain relief. They

injected 0.5 mL followed 10 seconds later by 2.5 mL followed 10 seconds later by 6 mL, so that the spreading patterns of different volumes could be compared. With 9 mL of injectate, the ventral dye spread was 2 vertebral bodies cranially and one caudally, versus only one vertebral body cranially with 3 mL of injectate.

Chun and Park (122) compared radicular pain relief at 3 and 8 mL of local anesthetic and steroid. They found better, almost 50%, pain relief at 4 weeks with 8 mL, compared with almost 30% pain relief with 3 mL.

Byun et al (125) found both 4 mL of local anesthetic/steroid and 4 mL of local anesthetic/steroid preceded by 5 mL of normal saline solution to be equally effective in treating radicular pain.

These data suggest that although the evidence is conflicting, one may get better relief with higher volumes. Although no study has discussed the differential relief between back and leg pain based on volume, some experts have suggested that lower volumes are effective for radicular pain, whereas higher volumes provide both low back and radicular relief.

Injections in the Age of COVID-19

The SARS-CoV-2 pandemic has highlighted the risk to patients of steroids. The Van Boxem et al (158) review, which was published prior to the pandemic, discusses issues related to steroid use in patients with COVID-19 infection. Chief among these is a dose-dependent suppression of the immune system, of greatest concern in those with concomitant disease or immunosuppression. The working group recommended that steroid doses be limited to 40 mg for methylprednisolone, 10 to 20 mg for triamcinolone, and 10 mg for dexamethasone.

The ASIPP Morbidity Risk Mitigation plan recommends, for at least phase I of the reopening of medical activity, either no steroids or the lowest dose possible (164).

The future may entail epidural steroid injections without steroids. The reviewed evidence supports this approach.

Limitations

Although there is a robust literature supporting the use of transforaminal epidural steroid injections for discogenic radicular pain, the literature for their use in stenosis or failed back surgery is limited. For axial low back pain not of facet or sacroiliac joint origin, there is no literature.

The meta-analysis was limited to a single-arm analysis of particulate and nonparticulate steroids.

Conclusions

Lumbar transforaminal injections have strong, Level 1, evidence supporting their use for discogenic radicular pain.

The evidence is Level IV for radicular pain from central stenosis or failed back surgery syndrome. The evidence is Level V for radicular pain from foraminal stenosis and from axial low back pain with no radicular component.

The strongest single step to avoid neural catastrophes is the use of blunt needles. In the absence of blunt needles, an infraradicular approach should be considered.

Either particulate or nonparticulate steroids may be used. If available, on-label epidural steroids would be preferred.

Steroids do not need to be used during transforaminal injections. Multiple options are open to physicians as to what might effectively be injected. High volumes may be more effective than low volumes.

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Appendix references and tables are available at www.painphysicianjournal.com

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

A	1. Was the method of randomization adequate?	Yes/No/Unsure
B	2. Was the treatment allocation concealed?	Yes/No/Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?	
	3. Was the patient blinded to the intervention?	Yes/No/Unsure
	4. Was the care provider blinded to the intervention?	Yes/No/Unsure
	5. Was the outcome assessor blinded to the intervention?	Yes/No/Unsure
D	Were incomplete outcome data adequately addressed?	
	6. Was the drop-out rate described and acceptable?	Yes/No/Unsure
	7. Were all randomized patients analyzed in the group to which they were allocated?	Yes/No/Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	Yes/No/Unsure
F	Other sources of potential bias:	
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	Yes/No/Unsure
	10. Were cointerventions avoided or similar?	Yes/No/Unsure
	11. Was the compliance acceptable in all groups?	Yes/No/Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Yes/No/Unsure

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 Updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (38).

Appendix Table 2. *Item checklist for assessment of RCTs of IPM techniques utilizing IPM–QRB. (43)*

		Scoring
I.	**CONSORT OR SPIRIT**	
1.	**Trial Design Guidance and Reporting**	
	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
	Computed tomography	2
	Fluoroscopy	3
5.	**Sample Size**	
	Less than 50 patients 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

Appendix Table 2. *Item checklist for assessment of RCTs of IPM techniques utilizing IPM–QRB. (43) (continued)*

		Scoring
	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
	Disorder 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
	>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 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 >20% reduction OR functional status improvement of > 20%	1
	Pain rating with decrease of ≥ 2 points AND ≥ 20% change or functional status improvement of ≥ 20%	2
12.	Analysis of All Randomized Patients in the Groups	
	Not performed	0
	Performed without intent-to-treat analysis without inclusion of all randomized patients	1
	All patients included with or without intent-to-treat analysis	2
13.	Description of Drop-Out Rate	
	No description of drop-outs, despite reporting of incomplete data or ≥20% withdrawal	0
	Less than 20% withdrawal in 1 year in any group	1
	Less than 30% withdrawal at 2 years in any group	2

Appendix Table 2. *Item checklist for assessment of RCTs of IPM techniques utilizing IPM–QRB. (43) (continued)*

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 Cointerventions	
	Cointerventions were provided but were not similar in the majority of patients	0
	No cointerventions or similar cointerventions were provided in the majority of the patients	1
V.	RANDOMIZATION	
16.	Method of Randomization	
	Quasi randomized or poorly randomized or not described	0
	Adequate randomization (coin toss, drawing of balls of different colors, drawing of ballots)	1
	High-quality randomization (computer-generated random sequence, preordered sealed envelopes, sequentially ordered vials, telephone call, preordered 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 MAXIMUM		48

Abbreviations: AHRQ, Agency for Healthcare Research and Quality; NHS, National Health Service; NIH, National Institutes of Health; PMR, Physical Medicine and Rehabilitation.

Appendix Table 3. *List of excluded randomized and nonrandomized studies.*

Study	Number of Patients	Treatment vs. Comparator	Follow-Up Period	Outcomes	Reason for Exclusion
RCTs					
Godek 2019 (61)	30	4 weekly collagen injections subcutaneous, periradicular, or epidural	1 month	VAS, ODI	< 50 patients < 6-month follow-up
Imani et al. 2019 (64)	30	TF with triamcinolone or dexmedetomidine	6 months	VAS, ODI	< 50 patients
Kim et al. 2018 (123)	50	Supraradicular vs. infraradicular high volume (9 mL) injections	1 month	Spreading pattern	< 6-month follow-up
El Maadawy et al. 2018 (62)	40	TF vs. IL vs. parasagittal	6 months	VAS, modified ODI	< 50 patients
Kennedy et al. 2018 (68)	78	TF	5 years	Presence of pain, opioid use, additional injections, progression to surgery	Same patient population as Kennedy et al. 2014 (81)
Mehta et al. 2017 (69)	120	TF, physical therapy	1 month	VAS	< 6-month follow-up
Lee et al. 2016 (73)	44	TF vs. pulsed radiofrequency of DRG	3 months	VAS, ODI	< 50 patients < 6-month follow-up
Chun and Park 2015 (122)	66	Low volume (3 mL) vs. high volume (8 mL) TF	1 month	VAS, RMDQ	< 6-month follow-up
Rezende et al. 2015 (74)	40	TF vs. IL	3 months	VAS	< 50 patients < 6-month follow-up
Cohen et al. 2015 (76)	145	TF vs. IL vs. sham injection and gabapentin	3 months		< 6-month follow-up
Hashemi et al. 2015 (66)	64	TF vs. IL	1 month	NRS, ODI	< 6-month follow-up
Friedly et al. 2014 (72)	386	IL and TF comparing lidocaine/steroid and lidocaine alone	1.5 months		< 6-month follow-up
Gupta et al. 2014 (102)	60	TF vs. IL vs. parasagittal	3 months	VAS	< 6-month follow-up
Byun et al. 2014 (125)	50	TF with dexamethasone 4 mg/3 mL 0.33% lidocaine vs. 5 mL NS and dexamethasone 4 mg/3 mL 0.33% lidocaine	4 weeks	VAS, modified McNabb scale	< 6-month follow-up
Freeman et al. 2013 (82)	49	Etanercept vs. placebo	6 months	Worst leg pain	< 50 patients
Nam and Park 2011 (84)	36	Local anesthetic and steroid vs. local anesthetic alone	3 months	VAS	< 50 patients < 6-month follow-up
Gharibo et al. 2011 (86)	42	TF vs. IL	0.5 months	NRS; ODI	< 50 patients < 6-month follow-up
Ahadian et al. 2011 (87)	98	Dexamethasone at 3 doses	3 months	VAS	< 6-month follow-up
Burgher et al. 2011 (89)	26	Lidocaine with clonidine or triamcinolone	6 months	NRS, RMDQ, ODI	< 50 patients
Kim et al. 2011 (124)	61	Supraradicular vs. infraradicular	2 weeks	VAS	< 6-month follow-up
Park et al. 2010 (90)	106	Particulate vs. nonparticulate steroid	1 month	VAS, ODI, Magill	< 6-month follow-up
Lee et al. 2007 (95)	108	Supraradicular vs. infraradicular injections	0.5 months	5-point patient outcome score	< 6-month follow-up
Ng et al. 2005 (97)	86	Local anesthetic/steroid vs. local anesthetic alone	3 months	VAS, ODI	< 6-month follow-up

Appendix Table 3 con't. ***List of excluded randomized and nonrandomized studies. (continued)***

Study	Number of Patients	Treatment vs. Comparator	Follow-Up Period	Outcomes	Reason for Exclusion
Thomas et al. 2003 (98)	31	Fluoroscopically guided TF vs. blind IL	6 months	VAS, RMDQ	< 50 patients
Nonrandomized Studies					
Farooque et al. 2017 (116)	26	Bilateral TF	6 months	VAS	< 50 patients
Maus et al. 2016 (114)	516	TF	2 months	NRS, RMDQ	< 6-month follow-up
Joswig et al. 2016 (113)	57	CT-guided TF	1 month	VAS	< 6-month follow-up
Tauheed et al. 2014 (80) RADIC	180	Methylprednisolone with or without clonidine	3 months	VAS	< 6-month follow-up
Ploumis et al. 2014 (111)	31	TF vs. caudal	6 months	VAS, ODI	< 50 patients
Rahimzadeh et al. 2014 (112)	25	TF with and without hyaluronidase	1 month	VAS, analgesic requirements	< 50 patients < 6-month follow-up
Mobaleghi et al. 2011 (85)	60	IL for RADIC and SS	6 months	NRS	IL injections only
Smith et al. 2010 (109)	19	TF vs. IL	1 month	VAS	< 50 patients < 6-month follow-up
Lee et al. 2009 (120)	95	TF vs. IL, caudal	2 months	NRS, RMDQ	< 6-month follow-up
Lee et al. 2009 (93)	192	TF vs. IL	4 months	NRS, patient satisfaction	< 6-month follow-up
Schaufele et al. 2006 (105)	40	TF vs. IL	12 months	NRS	< 50 patients
Yang et al. 2006 (106)	21	TF	23 months	JOA back score	< 50 patients
Botwin et al. 2002 (104)	34	TF	12 months	VAS, RMDQ	< 50 patients
Vad et al. 2002 (99)	48	TF vs. saline trigger point injections	> 1 year	VAS, RMDQ, patient satisfaction	< 50 patients
Viton et al. 1998 (101)	40	TF	3 months	VAS	< 50 patients < 6-month follow-up
Weiner and Fraser 1997 (103)	30	TF	3.4 years average	Low back outcome score, return to work	< 50 patients

Abbreviations: CT, computed tomography; DRG, dorsal root ganglion; IL, interlaminar injection; JOA, Japan Orthopaedic Association; NRS, Numeric Rating Scale; NS, normal saline; ODI, Oswestry Disability Index; RADIC, herniated nucleus pulposus/radicular pain; RMDQ, Roland Morris Disability Questionnaire; SS, spinal stenosis; TF, transforaminal injection; VAS, Visual Analog Scale.

Appendix Table 4. *Methodological quality assessment of randomized trials of therapeutic transforaminal epidural injections utilizing Cochrane Review criteria.*

Study Name	Wei et al. 2020 (63)	De et al. 2020 (67)	Makkar et al. 2019 (65)	Pandey 2016 (71)	Kamble et al. 2016 (115)	Denis et al. 2015 (75)	Ghai et al. 2014 (78)	Kennedy et al. 2014 (81)	Manchikanti et al. 2014 (77)
Randomization adequate	X	X	X		X	X	X	X	X
Concealed treatment allocation	X	X	X		X	X	X	X	X
Patient blinded	X	X	X		X	X	X	X	X
Care provider blinded		X	X		X	X	X	X	X
Outcomes assessor blinded		X	X		X	X	X	X	X
Drop-out rate described	X	X	X	X		X	X	X	X
All randomized patients analyzed in the group	X	X	X	X	X	X	X	X	X
Reports of the study free of suggestion of selective outcome reporting	X	X	X		X	X	X	X	X
Groups similar at baseline regarding most important prognostic indicators	X	X	X			X	X	X	X
Cointervention avoided or similar in all groups	X	X	X			X	X	X	X
Compliance acceptable in all groups	X	X	X	X		X	X	X	X
Time of outcome assessment in all groups similar	X	X	X	X	X	X	X	X	X
Score	10/12	12/12	12/12	4/12	8/12	12/12	11/12	11/12	12/12

Study Name	Cohen et al. 2012 (83)	Rados et al. 2011 (88)	Ghahreman et al. 2010 (91)	Tafazal et al. 2009 (92)	Jeong et al. 2007 (94)	Ackerman & Ahmad 2007 (107)	Bonetti et al. 2005 (96)	Karppinen et al. 2001 (60)	Devulder et al. 1999 (100)
Randomization adequate	X	X	X	X				X	
Concealed treatment allocation	X	X	X	X	X			X	X
Patient blinded	X	X	X	X	X			X	X
Care provider blinded	X			X				X	
Outcomes assessor blinded	X	X	X	X	X		X	X	
Drop-out rate described	X	X	X	X	X	X	X	X	
All randomized patients analyzed in the group	X	X	X	X	X	X	X	X	X
Reports of the study free of suggestion of selective outcome reporting	X	X	X	X	X	X	X	X	X
Groups similar at baseline regarding most important prognostic indicators	X	X	X	X	X	X	X	X	X
Cointervention avoided or similar in all groups	X	X	X			X		X	X
Compliance acceptable in all groups	X	X	X	X	X	X	X	X	X
Time of outcome assessment in all groups similar	X	X	X	X	X	X	X	X	X
Score	12/12	11/12	11/12	11/12	9/12	7/12	7/12	12/12	8/12

Appendix Table 5. *Methodologic quality assessment of randomized trials of therapeutic transforaminal epidural injections utilizing IPM–QRB criteria.*

Study Name		Wei et al. 2020 (63)	De et al. 2020 (67)	Makkar et al. 2019 (65)	Kamble et al. 2016 (115)	Denis et al. 2015 (75)	Ghai et al. 2014 (78)	Kennedy et al. 2014 (81)	Manchikanti et al. 2014 (77)
I.	Trial Design and Guidance Reporting								
1.	CONSORT or SPIRIT	0	3	3	0	2	3	2	3
II.	DesignFfactors								
2.	Type and design of trial	2	2	2	2	2	2	2	2
3.	Setting/physician	1	2	2	1	2	2	1	2
4.	Imaging	3	3	3	3	3	3	3	3
5.	Sample size	2	2	2	2	2	2	2	3
6.	Statistical methodology	1	1	1	1	1	1	1	1
III.	Patient Factors								
7.	Inclusiveness of population	2	2	2	0	2	2	2	2
8.	Duration of pain	0	1	1	0	0	1	1	1
9.	Previous treatments	2	2	2	2	1	1	2	2
10.	Duration of follow-up with appropriate interventions	1	1	1	1	1	2	1	3
IV.	Outcomes								
11.	Outcomes assessment criteria for significant improvement	2	1	2	0	2	2	2	4
12.	Analysis of all randomized patients in the groups	1	2	2	0	2	2	2	2
13.	Description of dropout rate	1	1	1	0	1	1	1	1
14.	Similarity of groups at baseline for important prognostic indicators	2	2	2	0	2	2	2	1
15.	Role of cointerventions	1	1	1	0	0	1	1	1
V.	Randomization								
16.	Method of randomization	2	2	2	2	2	2	2	2
VI.	Allocation Concealment								
17.	Concealed treatment allocation	2	2	2	2	2	2	2	2
VII.	Blinding								
18.	Patient blinding	1	1	1	0	1	1	1	1
19.	Care provider blinding	0	1	0	0	1	0	0	1
20.	Outcome assessor blinding	0	1	1	1	1	1	1	1
VIII.	Conflicts of Interest								
21.	Funding and sponsorship	2	2	2	2	2	2	2	2
22.	Conflicts of interest	3	3	3	3	3	3	0	3
Total		31/48	35/48	35/38	23/38	35/48	38/48	33/48	44/48

Appendix Table 5 con't. *Methodologic quality assessment of randomized trials of therapeutic transforaminal epidural injections utilizing IPM–QRB criteria. (continued)*

Study Name		Cohen et al. 2012 (83)	Rados et al. 2011 (88)	Ghahreman et al. 2010 (91)	Tafazal et al. 2009 (92)	Jeong et al. 2007 (94)	Ackerman & Ahmad 2007 (107)	Bonetti et al. 2005 (96)	Karppinen et al. 2001 (60)	Devulder et al. 1999 (100)
I.	Trial Design and Guidance Reporting									
1.	CONSORT or SPIRIT	2	2	2	0	0	0	0	1	1
II.	Design Factors									
2.	Type and design of trial	2	2	2	2	2	2	2	2	2
3.	Setting/physician	2	2	2	1	1	2	1	1	2
4.	Imaging	3	3	3	3	3	3	2	3	3
5.	Sample size	2	2	2	3	3	2	3	3	1
6.	Statistical methodology	1	1	1	1	1	1	1	1	1
III.	Patient Factors									
7.	Inclusiveness of population	2	2	2	1	2	2	0	2	2
8.	Duration of pain	0	0	1	0	0	0	0	0	2
9.	Previous treatments	2	2	0	2	0	0	1	0	2
10.	Duration of follow-up with appropriate interventions	1	1	2	2	2	1	1	2	2
IV.	Outcomes									
11.	Outcomes assessment criteria for significant improvement	2	1	2	1	2	1	2	2	2
12.	Analysis of all randomized patients in the groups	2	2	2	1	1	1	1	1	1
13.	Description of dropout rate	1	1	1	1	1	1	1	1	0
14.	Similarity of groups at baseline for important prognostic indicators	2	2	2	1	2	2	0	2	2
15.	Role of cointerventions	1	1	1	1	0	0	1	1	1
V.	Randomization									
16.	Method of randomization	2	2	2	2	0	0	0	2	0
VI.	Allocation Concealment									
17.	Concealed treatment allocation	2	2	2	2	2	1	1	2	1
VII.	Blinding									
18.	Patient blinding	1	1	1	1	1	0	1	1	0
19.	Care provider blinding	1	0	0	1	0	0	0	1	0
20.	Outcome assessor blinding	1	1	1	1	1	0	1	1	0
VIII.	Conflicts of Interest									
21.	Funding and sponsorship	2	2	2	0	2	2	0	2	2
22.	Conflicts of interest	3	3	0	0	2	1	0	3	0
Total		37/48	35/48	33/48	27/48	28/48	22/48	19/48	34/48	27/48

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 Updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (38).