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Systematic Review

The Effectiveness of Lumbar Interlaminar Epidural Injections in Managing Chronic Low Back and Lower Extremity Pain

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Background: Intervertebral disc herniation, spinal stenosis, intervertebral disc degeneration without disc herniation, and post lumbar surgery syndrome are the most common diagnoses of chronic persistent low back and lower extremity symptoms, resulting in significant economic, societal, and health care impact. Epidural injections are one of the most commonly performed interventions in the United States in managing chronic low back pain. However the evidence is highly variable among different techniques utilized – namely interlaminar, caudal, and transforaminal – and for various conditions, namely – intervertebral disc herniation, spinal stenosis, and discogenic pain without disc herniation or radiculitis. Multiple systematic reviews conducted in the evaluation of the effectiveness of interlaminar epidural injections have been marred with controversy. Consequently, the debate continues with regards to the effectiveness, indications, and medical necessity of interlaminar epidural injections.

Study Design: A systematic review of lumbar interlaminar epidural injections with or without steroids.

Objective: To evaluate the effect of lumbar interlaminar epidural injections with or without steroids in managing various types of chronic low back and lower extremity pain emanating as a result of disc herniation or radiculitis, spinal stenosis, and chronic discogenic pain.

Methods: The available literature on lumbar interlaminar epidural injections with or without steroids in managing various types of chronic low back pain with or without lower extremity pain was reviewed. The quality assessment and clinical relevance criteria utilized were the Cochrane Musculoskeletal Review Group criteria as utilized for interventional techniques for randomized trials and the criteria developed by the Newcastle-Ottawa Scale criteria for observational studies.

The level of evidence was classified as good, fair, or limited based on the quality of evidence developed by the U.S. Preventive Services Task Force (USPSTF).

Data sources included relevant literature identified through searches of PubMed and EMBASE from 1966 to December 2011, and manual searches of the bibliographies of known primary and review articles.

Outcome Measures: The primary outcome measure was pain relief (short-term relief = up to 6 months and long-term > 6 months). Secondary outcome measures were improvement in functional status, psychological status, return to work, and reduction in opioid intake.

Results: Overall, 82 lumbar interlaminar trials were identified. All non-randomized studies without fluoroscopy and randomized trials not meeting the inclusion criteria were excluded. Overall, 15 randomized trials and 11 non-randomized studies were included in the analysis. Analysis was derived mainly from fluoroscopically-guided randomized trials and non-randomized studies.

The evidence is good for radiculitis secondary to disc herniation with local anesthetics and steroids, fair with local anesthetic only; whereas it is fair for radiculitis secondary to spinal stenosis with local anesthetic and steroids, and fair for axial pain without disc herniation with local anesthetic with or without steroids, with fluoroscopically-guided epidural injections.

Limitations: The limitations of this study include that we were unable to perform meta-

analysis for disc herniation, and the paucity of evidence for discogenic pain and spinal stenosis. Further, methodological criteria have been highly variable along with sample sizes. The studies were heterogenous.

Conclusion: The evidence based on this systematic review is good for lumbar epidural injections under fluoroscopy for radiculitis secondary to disc herniation with local anesthetic and steroids, fair with local anesthetic only; whereas it is fair for radiculitis secondary to spinal stenosis with local anesthetic and steroids, and fair for axial pain without disc herniation with local anesthetic with or without steroids.

Key words: Chronic low back pain, lower extremity pain, disc herniation, radiculitis, spinal stenosis, discogenic pain, lumbar interlaminar epidural injections, fluoroscopy

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Rising incidences of chronic low back pain with or without lower extremity pain and explosive increases in volume and intensity of treatment modalities for management of low back pain are major strains on the health care system (1-40). The most invasive modality, surgery, is usually performed for the most common diagnosis for low back and leg pain: disc herniation, spinal stenosis, and degenerative spondylolisthesis (16,17,20,30,37,41-45). If conservative treatment fails, then surgery or epidural injections are commonly performed for chronic persistent pain of disc herniation with or without radiculitis, axial or discogenic pain without facet joint pain, spinal stenosis, and post lumbar surgery syndrome.

Epidural injections are administered by accessing the lumbar epidural space by multiple routes including interlaminar, caudal, and transforaminal (1,12,15,20,26,28,46-60). While significant differences have been described between these 3 approaches, interlaminar entry is considered to deliver the medication closely to the assumed site of pathology, even though the transforaminal approach is considered the target-specific modality requiring the smallest volume to reach the primary site of pathology (1,26,46-59). Caudal epidurals are considered as the safest and easiest with minimal risk of inadvertent dural puncture, and preferred modality in post surgery syndrome, even though requiring relatively high volumes (1,47).

The disadvantages also are multiple, which are described as lack of target specificity, the distribution of injectate into the dorsal space rather than ventrolateral space, lack of spread to multiple segments, excessive spread, and dural puncture. Multiple variations in the technique and the advantages and disadvantages of fluoroscopic display patterns have been described over the years (61-73). In a survey of the technical aspects of epidural steroid injections, Cluff et al (63) found only 30% of lumbar epidurals were performed under fluoroscopy in academic institutions; whereas, it was 77% in private practices. White et al (66) reported incorrect needle placement in 30.4% of patients when the lumbar interlaminar route was performed without fluoroscopy. Bartynski et al (68) described incorrect needle positioning during lumbar epidural steroid injection with loss of air pressure resistance in 25.7% of patients. Fredman et al (67) studied 50 patients with failed back surgery syndrome. The results showed that the epidural catheter did not pass through the predetermined intervertebral space in 35 cases and the contrast medium did not reach the level of pathology. Liu et al (69) prospectively evaluated with a 20-gauge Tuohy needle for lumbar epidural steroid injections and concluded that the success rate was only 92%.

Botwin et al (73) evaluated lumbar interlaminar epidural injections and epidurography pattern. They showed that dorsal contrast of flow occurred in 100% of injections; however, ventral spread of the contrast was seen only in 36% of the patients. They showed a unilateral filling pattern in 84% of the patients; whereas, it was bilateral in 16%. They also showed that the mean number levels of flow contrast cephalad from the injection site was 1.28 and caudally it was 0.88 with injection of a total of 5 mL of contrast. Weil et al (61) also evaluated fluoroscopic analysis of lumbar epidural contrast spread after lumbar interlaminar injection. They showed that the contrast spread was affected by needle placement, with other variables kept equal in performance, with the recommendation that fluoroscopy be used. They showed the spread was greater than one segment caudally more than 75% of the time under all variables. Anterior versus posterior epidural spread on the lateral view was approximately even over all cases and anterior spread was found more often when the needle was within the root of the distal spinous process tip. In another case report (62), for interlaminar epidural injections, using the loss of resistance technique and fluoroscopy without epidurogram, the rate of suboptimal injection was 12.3%. Candido et al (72)

evaluated fluoroscopically-guided lumbar epidural steroid injections and noted the epidural patterns with a lateral parasagittal approach and compared to a transforaminal approach. They reached the conclusion that the parasagittal interlaminar epidural approach was superior to the transforaminal approach.

Choi and Barbella (65) in an evaluation of contrast patterns of interlaminar epidural injections showed excellent spread of contrast into the nerve root and the ventral epidural space in all patients utilizing a paramedian approach. Whitlock et al (70) evaluated the influence of needle position on injectate spread with lumbar interlaminar injections in 460 patients. They concluded that epidural injection flow was highly variable, both among patients and between injections in a single patient. Midline injections were less likely to result in unilateral flow than a more lateral approach. Patients with previous spinal operations were more likely to have cephalad or caudad flow of less than one vertebral level than patients without a history of spinal operation. Rabinovitch et al (71) evaluated the influence of lumbar epidural injection volume on pain relief in a review of the existing literature. They showed a positive correlation between larger volumes of fluid injected into the epidural space and greater relief of radicular leg pain and/or low back pain. Identification of the epidural space with optical spectroscopy was described in a swine study with the conclusion that spectroscopic information obtained with the optical spinal needle is complementary to fluoroscopic measures, and it could potentially allow for reliable identification of the epidural space during needle placement.

Even though radicular artery injection and paralysis, etc. have been reported in multiple cases, there has been only one case report with interlaminar epidural injections (74). Much has been described about the radiculomedullary artery and its location (75). Major complications with spinal cord infarction have been described with transforaminal epidural injections in multiple reports (76-84).

Epidural procedures continue to be debated regarding their effectiveness, indications, and medical necessity (1,12,15,20,26-29,46-50). The highly variable evidence ranged from indeterminate to moderate in multiple publications. The first systematic review of the effectiveness of epidural steroid injections was performed by Kepes and Duncalf in 1985 (51) which concluded that the rationale for epidural and systemic steroids had not been proven. However, in a follow-up systematic review in 1986, Benzon (59), utilizing the same studies, concluded that mechanical causes of low back pain, especially those accompanied by signs of nerve root irritation, may respond to epidural steroid injections. The differences in the conclusions of Kepes and Duncalf (51) and Benzon (59) may have been due to the fact that Kepes and Duncalf (51) included studies on systematic steroids, whereas Benzon (59) limited his analysis to studies on epidural steroid injections only.

Bogduk et al (26) concluded that the results of lumbar interlaminar epidural steroids strongly refute the utility of epidural steroids in acute sciatica. Bogduk (50) updated their recommendations in 1999, recommending against epidural steroids by the lumbar route because effective treatment required too high a number for successful treatment. In 1995, Koes et al (52) reviewed 12 trials of lumbar and caudal epidural steroid injections (combined together) and reported positive results from only 6 studies, concluding that there was no evidence for epidural steroids in managing lumbar radicular pain. Their updated review (53) with 15 trials arrived at similar conclusions that there was no evidence that epidural steroid injections are effective in patients with chronic back pain without sciatica.

Watts and Silagy (54), in a meta-analysis of the efficacy of epidural corticosteroids in the treatment of sciatica, utilized 11 studies considered of good quality, involving a total of 907 patients, and concluded that quantitative evidence from meta-analysis of pooled data from randomized trials illustrated that epidural administration of corticosteroids was effective in the management of lumbosacral radicular pain

Staal et al (15) in an updated Cochrane Review of injection therapy for subacute and chronic low back pain concluded that there was insufficient evidence to support the use of epidural injections in managing chronic low back pain. However, they concluded that it cannot be ruled out that specific subgroups of patients may respond to a specific type of injection therapy. Armon et al (56) in an assessment of the use of epidural steroid injections to treat radicular lumbosacral pain, in a poorly performed evaluation, concluded that in general, epidural steroid injections for radicular lumbosacral pain do not impact average impairment of function, need for surgery, or provide long-term pain relief beyond 3 months with a negative recommendation (20,60).

Parr et al (46) reviewed the effectiveness of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain. The results showed that the available literature included only blind epi-

dural injections without fluoroscopy. Consequently, the evidence was determined as poor.

The American Pain Society (APS) guidelines by Chou and Huffman also showed negative results for lumbar interlaminar epidural injections except for radicular pain on a short-term basis (20,28). Rho and Tang (85) in describing the efficacy of lumbar epidural steroid injections, which also included all 3 approaches, showed strong evidence for transforaminal epidural steroid injections, but the evidence showed only short-term efficacy of interlaminar epidural steroid injections and caudal epidural injections in the management of low back and radicular pain. They concluded that lumbar epidural steroids can be an effective tool in the conservative management of low back pain with radicular symptoms. Multiple evaluators in the past have reached favorable conclusions with moderate effectiveness in managing lumbar radiculopathy, when these were separated from blind interlaminar epidural injections. There is also emerging evidence with studies under fluoroscopy.

Due to the ongoing debate and lack of significant evidence, this systematic review is undertaken to evaluate the effects of lumbar interlaminar epidural injections in managing chronic low back and lower extremity pain secondary to lumbar disc herniation and radiculitis, spinal stenosis, and chronic low back pain of discogenic origin without radiculitis or disc herniation.

1.0 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 (1,15,86-96), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (97-100), Standards for Reporting Observational Studies (STROBE) (101), Cochrane guidelines (15,91,92), Chou and Huffman's guidelines (20), and quality of reporting of analysis (88).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Studies

Randomized controlled trials
Non-randomized observational studies
Case reports and reviews for adverse effects

1.1.2 Types of Participants

Participants of interest were adults aged at least 18 years with chronic low back and lower extremity pain of at least 3 months duration.

Participants must have failed previous pharmacotherapy, exercise therapy, etc., prior to starting interventional pain management techniques.

1.1.3 Types of Interventions

The interventions were lumbar interlaminar epidural injections for chronic low back and/or lower extremity pain. All randomized trials with proper inclusion criteria and appropriately performed non-randomized studies with proper technique under fluoroscopic or CT guidance.

1.1.4 Types of Outcome Measures

- The primary outcome parameter was pain relief.
- The secondary outcome measures were functional improvement; change in psychological status; return to work; reduction or elimination of opioid use, other drugs, or other interventions; and complications.
- At least 2 of the review authors independently, in an unblinded standardized manner, assessed the outcomes measures. Any disagreements between reviewers were resolved by a third author and consensus.

1.2 Literature Search

Searches were performed from the following sources without language restrictions:

1. PubMed from 1966
   www.ncbi.nlm.nih.gov/sites/entrez?db=pubmed
2. EMBASE from 1980
   www.embase.com
3. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
4. U.S. National Guideline Clearinghouse (NGC)
   www.guideline.gov
5. Previous systematic reviews and cross references
6. Clinical Trials
   www.clinicaltrials.gov

The search period was from 1966 through December 2011.

1.3 Search Strategy

The search strategy emphasized chronic low back and lower extremity pain, disc herniation, discogenic pain, spinal stenosis, and radiculitis treated with lumbar interlaminar epidural injections.

At least 2 of the review authors independently, in an unblinded standardized manner, performed each search. Accuracy was confirmed by a statistician. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and consensus.

1.4 Data Collection and Analysis

The review focused on randomized trials, fluoroscopically-guided observational studies, and reports of complications. The population of interest was patients suffering with chronic low back and lower extremity pain for at least 3 months. Only lumbar interlaminar epidural injections with or without steroids were evaluated. All of the studies providing appropriate management and with outcome evaluations of one month or longer and statistical evaluations were reviewed. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports will be excluded.

1.4.1 Selection of Studies

- In an unblinded, standardized manner, 2 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.

1.4.2 Inclusion and Exclusion Criteria

The following are the inclusion and exclusion criteria:

1. Are the patients described in sufficient detail to allow one to decide whether they are comparable to those who are treated in interventional pain management clinical practices?
   A. Setting – office, hospital, outpatient, inpatient
   B. Physician – interventional pain physician, general physician, anesthesiologist, physiatrist, neurologist, rheumatologist, orthopedic surgeon, neurosurgeon, etc.
   C. Patient characteristics - duration of pain
   D. Non-interventional techniques or surgical intervention in the past
2. Is the intervention described in sufficient detail to enable one to apply its use to patients in interventional pain management settings?
   A. Nature of intervention
   B. Frequency of intervention
   C. Duration of intervention
3. Were clinically relevant outcomes measured?
   A. Proportion of pain relief
   B. Disorder/specific disability
   C. Functional improvement
   D. Allocation of eligible and non-eligible patients to return to work
   E. Ability to work

1.4.3 Clinical Relevance

The clinical relevance of the included studies were evaluated according to 5 questions recommended by the Cochrane Back Review Group (Table 1) (90,102). Each question was scored as positive (+) if the clinical relevance item was met, negative (–) if the item was not met, and unclear (?) if data were not available to answer the question.

Table 1. *Clinical relevance questions.*

	P (+)	N (-)	U (unclear)
A) Are the patients described in detail so that one can decide whether they are comparable to those who are treated in a clinical practice?			
B) Are the interventions and treatment settings described in sufficient detail to apply its use in clinical practice?			
C) Were clinically relevant outcomes measured and reported?			
D) Is the size of the effect clinically meaningful?			
E) Do the likely treatment benefits outweigh the potential harms?			

Scoring adapted and modified from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (102).

1.4.4 Methodological Quality or Validity Assessment

Even though none of these instruments or criteria have been systematically assessed, the advantages and disadvantages of each system were debated.

The methodological quality assessment was performed by 2 review authors who independently assessed, in an unblinded standardized manner, the internal validity of all the studies.

Any discrepancies or conflicts were arbitrated by a third reviewer to either reach a consensus agreement or break a tie. If there was a conflict of interest with the reviewed manuscripts with authorship or any other type of conflict, the involved authors did not review the manuscripts for quality assessment or evidence synthesis.

The quality of each individual article used in this analysis was assessed by Cochrane review criteria (Table 2) (91) for randomized trials and Newcastle-Ottawa Scale for observational studies (Tables 3 and 4) (103,104). For nonrandomized observational studies, the patient population should have had at least 50 total or at least 25 in each group if they were comparison groups.

Authors with a perceived conflict of interest for any manuscript were recused from reviewing the manuscript.

For adverse effects, confounding factors, etc., it was not possible to use quality assessment criteria. Thus, these were considered based on interpretation of the reports published and critical analysis of the literature.

Only the randomized trials meeting the inclusion criteria with at least 50% of the criteria were utilized for analysis. However, studies scoring lower were described and provided with an opinion and critical analysis.

Observational studies had to meet a minimum of 50% of the criteria for cohort and case-control studies. Studies scoring less were also described and provided with an opinion and a critical analysis.

If the literature search provided at least 5 randomized trials meeting the inclusion criteria and they were homogenous for each modality and condition evaluated, a meta-analysis was performed.

All lumbar interlaminar epidural injections were also evaluated separately for disc herniation, discogenic pain, and spinal stenosis.

1.4.5 Data Extraction and Management

Two review authors independently, in an unblinded standardized manner, extracted the data from the included studies. Disagreements were resolved by discussion between the 2 reviewers; if no consensus could be reached, a third author was called in to break the impasse.

1.4.6 Assessment of Heterogeneity

Whenever meta-analyses were conducted, the I-squared (I2) statistic was used to identify heterogeneity (104). Combined results with I2 > 50% were considered substantially heterogenous.

Analysis of the evidence was based on the condition (i.e., disc herniation or spinal stenosis) to reduce any clinical heterogeneity.

1.4.7 Measurement of Treatment Effect in Data Synthesis (Meta-Analysis)

Data was summarized using meta-analysis when at least 5 studies per type of disorder were available that met the inclusion criteria (e.g., lumbar disc herniation or spinal stenosis, etc.).

Qualitative (the direction of a treatment effect) and quantitative (the magnitude of a treatment effect) conclusions were evaluated. Random-effects meta-analysis to pool data was also used (105).

The minimum amount of change in pain score to be clinically meaningful has been described as a 2-point change on a scale of 0 to 10 (or 20 percentage points), based on findings in trials studying general chronic pain (106), chronic musculoskeletal pain (107), and chronic low back pain (86-88,90,107-109), which have been commonly utilized. However, recent descriptions of clinically meaningful improvement showed either pain relief or functional status as 50% (110-120). Consequently, for this analysis, we utilize clinically meaningful pain relief of at least a 3-point change on an 11-point scale of 0 to 10, or 50% pain relief from the baseline, as clinically significant, and functional status improvement of 40% or more.

1.4.8 Integration of Heterogeneity

The evidence was assessed separately by administration to each condition. A meta-analysis was performed only if there were at least 5 studies meeting inclusion criteria for each variable.

Statistical heterogeneity was explored using univariate meta-regression (121).

1.4.9 Software Used for Measurement

The data was analyzed using SPSS Version 9.0.1 statistical software (SPSS Inc., Chicago, IL), Microsoft Ac-

Table 2. *Randomized controlled trials quality rating system.*

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a die (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/ Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure
	5. Was the outcome assessor blinded to the intervention?	Adequacy of blinding should be assessed for the primary outcomes. This item should be scored "yes" if the success of blinding was tested among the outcome assessors and it was successful or: –for patient-reported outcomes in which the patient is the outcome assessor (e.g., pain, disability): the blinding procedure is adequate for outcome assessors if participant blinding is scored "yes" –for outcome criteria assessed during scheduled visit and that supposes a contact between participants and outcome assessors (e.g., clinical examination): the blinding procedure is adequate if patients are blinded, and the treatment or adverse effects of the treatment cannot be noticed during clinical examination –for outcome criteria that do not suppose a contact with participants (e.g., radiography, magnetic resonance imaging): the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed when assessing the main outcome –for outcome criteria that are clinical or therapeutic events that will be determined by the interaction between patients and care providers (e.g., co-interventions, hospitalization length, treatment failure), in which the care provider is the outcome assessor: the blinding procedure is adequate for outcome assessors if item "4" (caregivers) is scored "yes" –for outcome criteria that are assessed from data of the medical forms: the blinding procedure is adequate if the treatment or adverse effects of the treatment cannot be noticed on the extracted data.	Yes/No/ Unsure
D	Were incomplete outcome data adequately addressed?		
	6. Was the drop-out rate described and acceptable?	The number of participants who were included in the study but did not complete the observation period or were not included in the analysis must be described and reasons given. If the percentage of withdrawals and drop-outs does not exceed 20% for short-term follow-up and 30% for long-term follow-up and does not lead to substantial bias a "yes" is scored. (N.B. these percentages are arbitrary, not supported by literature).	Yes/No/ Unsure
	7. Were all randomized participants analyzed in the group to which they were allocated?	All randomized patients are reported/analyzed in the group they were allocated to by randomization for the most important moments of effect measurement (minus missing values) irrespective of non-compliance and co-interventions.	Yes/No/ Unsure
E	8. Are reports of the study free of suggestion of selective outcome reporting?	In order to receive a "yes," the review author determines if all the results from all pre-specified outcomes have been adequately reported in the published report of the trial. This information is either obtained by comparing the protocol and the report, or in the absence of the protocol, assessing that the published report includes enough information to make this judgment.	Yes/No/ Unsure
F	Other sources of potential bias:		
	9. Were the groups similar at baseline regarding the most important prognostic indicators?	In order to receive a "yes," groups have to be similar at baseline regarding demographic factors, duration and severity of complaints, percentage of patients with neurological symptoms, and value of main outcome measure(s).	Yes/No/ Unsure
	10. Were co-interventions avoided or similar?	This item should be scored "yes" if there were no co-interventions or they were similar between the index and control groups.	Yes/No/ Unsure
	11. Was the compliance acceptable in all groups?	The reviewer determines if the compliance with the interventions is acceptable, based on the reported intensity, duration, number and frequency of sessions for both the index intervention and control intervention(s). For example, physiotherapy treatment is usually administered over several sessions; therefore, it is necessary to assess how many sessions each patient attended. For single-session interventions (e.g., surgery), this item is irrelevant.	Yes/No/ Unsure
	12. Was the timing of the outcome assessment similar in all groups?	Timing of outcome assessment should be identical for all intervention groups and for all important outcome assessments.	Yes/No/ Unsure

Adapted and modified from Furlan AD, et al; 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 (91).

Table 3. Newcastle-Ottawa quality assessment scale for case control studies.

Selection
1) Is the case definition adequate?
a) yes, with independent validation *
b) yes, e.g. record linkage or based on self reports
c) no description
2) Representativeness of the cases
a) consecutive or obviously representative series of cases *
b) potential for selection biases or not stated
3) Selection of controls
a) community controls *
b) hospital controls
c) no description
4) Definition of controls
a) no history of disease (endpoint) *
b) no description of source
Comparability
1) Comparability of cases and controls on the basis of the design or analysis
a) study controls for _____ (Select the most important factor.) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Exposure
1) Ascertainment of exposure
a) secure record (eg surgical records) *
b) structured interview where blind to case/control status *
c) interview not blinded to case/control status
d) written self report or medical record only
e) no description
2) Same method of ascertainment for cases and controls
a) yes *
b) no
3) Non-response rate
a) same rate for both groups *
b) non respondents described
c) rate different and no designation

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability.

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (103).

Table 4. *Newcastle-Ottawa quality assessment scale for cohort studies.*

Selection
1) Representativeness of the exposed cohort
a) truly representative of the average _____ (describe) in the community *
b) somewhat representative of the average _____ in the community *
c) selected group of users, e.g. nurses, volunteers
d) no description of the derivation of the cohort
2) Selection of the non exposed cohort
a) drawn from the same community as the exposed cohort *
b) drawn from a different source
c) no description of the derivation of the non exposed cohort
3) Ascertainment of exposure
a) secure record (e.g. surgical records) *
b) structured interview *
c) written self report
d) no description
4) Demonstration that outcome of interest was not present at start of study
a) yes *
b) no
Comparability
1) Comparability of cohorts on the basis of the design or analysis
a) study controls for _____ (select the most important factor) *
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)
Outcome
1) Assessment of outcome
a) independent blind assessment *
b) record linkage *
c) self report
d) no description
2) Was follow-up long enough for outcomes to occur
a) yes (select an adequate follow-up period for outcome of interest) *
b) no
3) Adequacy of follow-up of cohorts
a) complete follow-up - all subjects accounted for *
b) subjects lost to follow-up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow-up, or description provided of those lost) *
c) follow-up rate < ____% (select an adequate %) and no description of those lost
d) no statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for Comparability.

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (103).

cess 2003, and Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) (122).

Meta-analyses were performed with Comprehensive Meta-Analysis Software Version 2.0 for Windows (Biostat Inc., Englewood, NJ) (123).

1.5 Summary Measures

Summary measures included 50% or more reduction of pain in at least 40% of the patients, or at least a 3 point decrease in pain scores and a relative risk of adverse events including side effects.

1.6 Analysis of Evidence

The analysis of the evidence was performed based on United States Preventive Services Task Force (USPSTF) criteria as illustrated in Table 5, criteria which has been utilized by multiple authors (19,20,22,95,96,124).

The analysis was conducted using 3 levels of evidence ranging from good, fair, or limited.

At least 2 of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and consensus. If there were any conflicts of interest (e.g., authorship), those reviewers were recused from assessment and analysis.

1.7 Outcome of the Studies

In the randomized trials, a study was judged to be positive if the lumbar interlaminar epidural injection therapy was clinically relevant and effective, either with a placebo control or active control. This indicates that the difference in effect for the primary outcome measure is statistically significant on the conventional 5% level. In a negative study, no difference between the study treatments or no improvement from baseline is identified. Further, the outcomes were judged at the reference point with positive or negative results reported at one month, 3 months, 6 months, and one year.

For observational studies, a study was judged to be positive if the epidural injection therapy was effective, with outcomes reported at the reference point with positive or negative results at one month, 3 months, 6 months, and one year. However, observational studies were only included in the evidence synthesis if there was less than 5 randomized trials meeting inclusion criteria for evidence synthesis for each condition (i.e., disc herniation, spinal stenosis, and discogenic pain).

2.0 Results

Figure 1 shows a flow diagram of study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (89). There were 82 studies considered for inclusion (72,110,111,117,118,125-199).

Of the 82 lumbar epidural trials identified, 54 were excluded (117,118,125-127,131,132,134,137,138,143,146,148-150,152,154-164,166-173,175,176-178,183-193,195-197). Table 6 shows the reasons for exclusion for lumbar interlaminar randomized trials and fluoroscopically-guided observational studies. Of these, only 15 were randomized trials (125-127,131,132,134,137,143,148,150,162,167,170,184,197) and 11 were non-randomized studies (138,149,163,164,169,172,173,175,178,183,193). The remaining non-randomized studies were performed without fluoroscopy (146,152,154-161,171,185-187).

Table 7 illustrates the characteristics of randomized trials without fluoroscopy considered for in-

Table 5. *Method for grading the overall strength of the evidence for an intervention.*

Grade	Definition
Good	Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes (at least 2 consistent, higher-quality RCTs or studies of diagnostic test accuracy).
Fair	Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, size, or consistency of included studies; generalizability to routine practice; or indirect nature of the evidence on health outcomes (at least one higher-quality trial or study of diagnostic test accuracy of sufficient sample size; 2 or more higher-quality trials or studies of diagnostic test accuracy with some inconsistency; at least 2 consistent, lower-quality trials or studies of diagnostic test accuracy, or multiple consistent observational studies with no significant methodological flaws).
Limited or poor	Evidence is insufficient to assess effects on health outcomes because of limited number or power of studies, large and unexplained inconsistency between higher-quality trials, important flaws in trial design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

Adapted and modified from methods developed by U.S. Preventive Services Task Force (19,20,124).

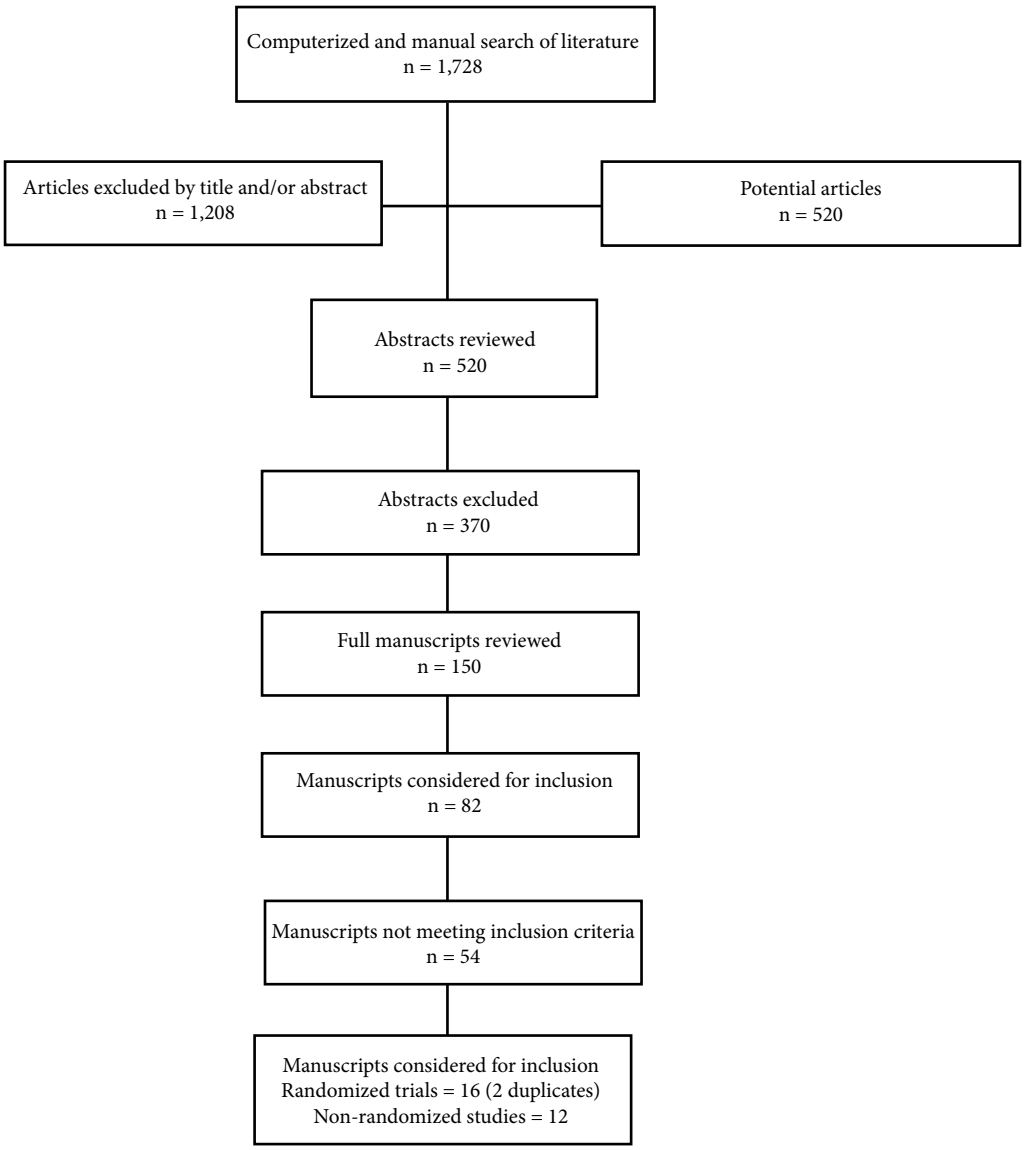

Fig. 1. *The flow diagram illustrating published literature evaluating lumbar interlaminar epidural injections.*

clusion. There were 12 randomized trials without fluoroscopy (128-130,133,135,136,139-142,144,153). Table 8 illustrates characteristics of 16 randomized trials and non-randomized studies performed under fluoroscopy (72,110,111,145,147,151,165,174,177,179-182,194,198,199) with 2 duplicate studies (110,111,198,199).

2.1 Clinical Relevance

Of the 26 studies assessed for clinical relevance, 23 randomized studies met criteria with score of 3 of 5 or greater (Table 9).

2.2 Methodological Quality Assessment

A methodological quality assessment of the randomized controlled trials meeting inclusion criteria was

Table 6. *List of excluded randomized trials and fluoroscopic non-randomized studies*

Manuscript Author(s)	Condition Studied	Number of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
RANDOMIZED				
Serrao et al (125)	Chronic low back pain	28	2 months	Intrathecal midazolam compared with epidural steroid in a pilot study.
Rodriguez Hernandez et al (126)	Diabetic neuropathy	20	30 days	Study of diabetic neuropathy with epidural steroid injections.
Kikuchi et al (127)	Postherpetic neuralgia	25	24 weeks	Comparison of intrathecal versus epidural methylprednisolone in intractable postherpetic neuralgia in a small number of patients.
Klenerman et al (131)	Sciatica	74	NA	The inclusion criteria was unilateral sciatica for less than 6 months, thus including acute and subacute patients.
Rocco et al (132)	Postlaminectomy syndrome	24	30 days	The effect of epidural steroids was compared with morphine in the treatment of postlaminectomy syndrome in only 24 patients.
Valat et al (134)	Lumbar radiculitis	85	35 days	The inclusion criteria was of sciatica of more than 15 and less than 180 days, thus including subacute and acute patients with sciatica.
Bronfort et al (137)	Lumbar radiculitis	32	52 weeks	The study included acute and subacute pain in patients in a small sample.
Snoek et al (143)	Lumbar disc herniation	51	14 months	Authors evaluated a single epidural injection in acute and subacute radiculitis. The inclusion criteria was with patients with lumbar root compression syndrome of 12 days to 36 weeks duration, thus including a number of acute and subacute pain patients.
Jirarattanaphochai et al (148)	Lumbar disc herniation	103	2 days	Authors evaluated peridural methylprednisolone and wound infiltration with bupivacaine for post-operative pain control after posterior lumbar spine surgery.
Price et al (150)	Chronic low back pain	200	Immediate	Comparison of accuracy of needle placement.
Rasmussen et al (162)	Disc herniation	200	One year	Authors evaluated epidural steroid following discectomy for herniated lumbar disc and concluded that epidural methylprednisolone enhances recovery after discectomy for herniated disc disease without side effects.
Lima et al (167)	Experimental trial in dogs	14 dogs	21 days	An animal basic science trial to evaluate clinical and histological effects of the intrathecal administration of methylprednisolone in dogs.
Debi et al (170)	Disc herniation	70	One year	Authors evaluated local application of steroids following lumbar discectomy.
Gelalis et al (184)	Lumbar disc herniation	40	2 months	Lumbar radiculitis secondary to acute and subacute pain was evaluated.
Mobaleghi et al (197)	Disc herniation and stenosis	60. Disc herniation = 32. Stenosis = 28	6 months	Blind prospective evaluation.
NON-RANDOMIZED				
Briggs et al (138)	Spinal stenosis	62	2 years	Lumbar interlaminar – appropriate data not available.
Schaufele et al (149)	Lumbar disc herniation	20	One year	A small number of patients with comparison of interlaminar versus transforaminal epidural injections in a case-control report.
Mitra et al (163)	Spinal stenosis	One	NA	A single case report of overactive bladder associated with severe central canal stenosis was studied.
Stretanski (164)	Lumbar radiculitis	10	One week	In this study, H-reflex latency and nerve root tension sign correlation was evaluated in 10 patients in a prospective observational report.

Table 6 (cont.). *List of excluded randomized trials and non-randomized studies performed under fluoroscopy.*

Manuscript Author(s)	Condition Studied	Number of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
Price et al (169)	Sciatica	228	52 weeks	This is a publication of another publication evaluating the cost-effectiveness and safety.
Furman et al (172)	Lumbar radiculitis	21	6 weeks	A small number of patients in a pilot study.
Smith et al (173)	Symptomatic lumbar spinal stenosis	38	6 weeks	A small retrospective analysis.
Noe & Haynsworth (175)	Low back pain	50	One month	Epidural depo-Medrol was compared with aqueous betamethasone in a retrospective evaluation.
Lee et al (178)	Lumbosacral herniated disc and spinal stenosis	58	2 years	It appears that the data of the study is derived from other studies with 38 patients in the non-invasive group and 20 patients in the epidural injection group.
Gharibo et al (183)	Lumbar radiculitis	42	3 weeks	Evaluation was conducted to look at interlaminar versus transforaminal epidural steroids for the treatment of subacute lumbar radicular pain.
Kapoor et al (193)	Lumbar radiculopathy	One	NA	Authors described in a case-report the gadolinium encephalopathy after intrathecal gadolinium injection.

carried out utilizing Cochrane review criteria as shown in Tables 10 and 11. Studies achieving Cochrane scores of 9 or higher were considered as high quality, 6 to 8 were considered as moderate quality, and studies scoring less than 6 were excluded.

There were 12 randomized trials (110,111,133, 136,139,140,142,144,147,153,179,180,198,199) scoring high quality, 8 scored moderate quality (72,128, 130, 135,141,165,174,181), and 3 were of low quality (129,177,194).

Among the fluoroscopically-guided randomized controlled trials 7 were of high quality (110,111,147,179,180,198,199) with 2 duplicate publications (111,112,199,200), 4 were of moderate quality (71,165,174,181), and 2 were of low quality (177,194). Among the non-fluoroscopic randomized trials, 7 were of high quality (133,136,139,140,142,144,153), 4 were of moderate quality (128,129,135,141), and one was of low quality (129).

A methodological quality assessment of the observational studies meeting inclusion criteria was carried out utilizing Newcastle-Ottawa Scales as illustrated in Table 12. For cohort studies, studies achieving scores of 10 or higher were considered high quality; 7 to 9 were considered moderate quality; studies scoring less than 7 were considered low quality and were excluded. There were no case control studies.

Among the non-randomized studies, the methodological quality assessment indicated no high quality studies, 2 were considered of moderate quality (145,151), and 1 was considered as low quality (182).

2.3 Meta-Analysis

Among the 11 randomized trials evaluating the role of epidural injections in disc herniation without fluoroscopy (128-130,133,135,136,139-142,144) 5 were placebo control (130,135,139,140,144); one placebo controlled study evaluated the role of epidural injections in spinal stenosis (153). In reference to the active controlled trials, there were 7 trials all evaluating the role of disc herniation (128,129,133,135,136,141,142). There were 3 placebo controlled trials evaluating injection of sodium chloride solution into the interspinous ligament compared with epidural steroid injection (130,139,144). One study assessed paravertebral steroid versus epidural steroid (135). Another study (140) assessed epidural saline versus epidural steroid. The study in spinal stenosis (155) assessed epidural saline versus

Table 7. *Assessment and description of study characteristics of randomized trials for inclusion criteria without fluoroscopy.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Buchner et al (128)	R, B, AC	X			36	Control group received a standard program of graded rehabilitation and physiotherapy. The treatment group received 3 lumbar epidural injections of 100 mg of methylprednisolone in 10 mL of bupivacaine, 0.25%	6 months	VAS and Hannover Functional Ability Questionnaire	This is a small study with 17 patients in the methylprednisolone group and 19 patients in the control group. Results showed better results in the methylprednisolone group, even though not statistically significant for pain relief and mobility.
McGregor et al (129)	R, B, AC	X			44	For caudal or lumbar interlaminar epidural - 15 or 10 mL of 0.5% bupivacaine, 100 mg of hydrocortisone in sterile water, and 5 mL of normal saline.	6 months	VAS, SF-36, ODI, EuroQol	Both injections were performed blindly with a short-term follow-up in a small number of patients with no statistically significant changes in either group irrespective of injection route in the ODI.
Dilke et al (130)	R, B, PC	X			100	Control group patients received an injection into the intraspinous ligament of 1 mL of normal saline, after preliminary local anesthesia. Treatment group received epidural injection of 80 mg of methylprednisolone in 10 mL normal saline.	3 months	Pain relief, analgesic consumption, changes in straight leg raising, or neurological signs	The results illustrated statistically highly significant differences in respect of relief of pain and resumption of normal occupation in favor of the group treated.
Rogers et al (133)	R, B, AC	X			30	Control group received 14 mL of 2% lignocaine with 6 mL of normal saline. Treatment group received same volumes with 2% lignocaine 14 mL, 2 mL of 80 mg of methylprednisolone and 4 mL of normal saline.	One month	Follow-up pain score, work status, analgesic consumption, straight leg raising	A small prospective randomized single-blind sequential analysis study of 30 patients showed epidural injection of steroid together with local anesthetic produced significantly better results than lumbar epidural injection of local anesthetic alone.
Kraemer et al (135)	R, B, AC, PC	X			133 Epidural = 40 Perineural = 47 Paravertebral = 46	One mL of local anesthetic and 10 mg of triamcinolone.	3 months	Pain relief, return to work, avoidance of surgery	Epidural groups had better results than paravertebral local injection group. Epidural perineural injections were more effective than saline alone. A systemic steroid effect was excluded by additional intramuscular steroid injections in the saline group.

Table 7 (cont.). *Assessment and description of study characteristics of randomized trials for inclusion criteria without fluoroscopy.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Pirbudak et al (136)	R, B, AC	X			92	Group I received 10 mL of solution which consisted of 10 mL of betamethasone and 0.25% bupivacaine. The second group also received the single dose of 10 mg per day amitriptyline to a maximum of 50 mg per day. Group I received placebo.	9 months	VAS, ODI	At 6 weeks, recovery was earlier in Group II receiving amitriptyline and fewer repeat injections were necessary. At 9 months, Group I did not statistically differ from the baseline values, while Group II had statistical improvement.
Arden et al (139)	R, B, PC	X			228	The control group received injection of 1 mL of normal saline into the interspinous ligament; whereas the treatment group received 80 mg of depo methylprednisolone and 10 mL of normal saline.	One year	ODQ, pain relief, VAS, SF-36	Authors included a number of patients who were of subacute or acute pain. At 3 weeks, the epidural steroid injection group demonstrated transient benefit over the placebo group with patients achieving a 75% improvement in ODQ. No benefit was demonstrated from 6 to 52 weeks.
Carette et al (140)	R, B, PC	X			158	The placebo group received one mL of isotonic saline, whereas treatment group received 80 mg of methylprednisolone in 8 mL of isotonic saline.	One year	VAS and ODI	At 3 weeks, there was significant improvement in patients receiving the steroids. After 6 weeks, the only significant difference was in the improvement in leg pain which was greater in the methylprednisolone group. After 3 months, there were no significant differences.
Cuckler et al (141)	R, B, AC	X		X	Total = 73 Disc herniation = 36 Spinal stenosis = 37	Either 2 mL of saline combined with 5 mL of 1% procaine or 2 mL of sterile water containing 80 mg of methylprednisolone acetate combined with 5 mL of 1% procaine.	13 to 30 months	75% improvement	In this study, 2 types of patients were evaluated, one with acute herniated nucleus pulposus with 22 patients in the steroid group and 14 in the placebo group; whereas in the spinal stenosis group, there were 20 patients in the steroid group and 17 in the local anesthetic group which they described as placebo.
Wilson-MacDonald et al (142)	R, B, AC	X		X	Total = 92 Disc herniation = 43 Spinal stenosis = 32	Either an intramuscular injection in the epidural area or epidural injection with bupivacaine 0.5%, 8 mL, with methylprednisolone 80 mg.	2 years	Oxford Pain Chart and ODI	There was a significant reduction in pain early on in those having an epidural steroid injection, but no difference in the long-term between the 2 groups. The rate of subsequent operation in the groups was similar. Consequently, there was expected relief in spite of multiple issues related to the study with short-term relief with a single epidural.

Table 7 (cont.). *Assessment and description of study characteristics of randomized trials for inclusion criteria without fluoroscopy.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Ridley et al (144)	R, B, PC	X			39	The control group received an interspinous injection of 2 mL of physiological saline. Treatment group received an epidural injection of 80 mg of methylprednisolone in 10 mL of physiological saline.	6 months	VAS, SLR	This was a small study of 39 patients without injection of local anesthetic with only methylprednisolone; however, there was significant differences between the 2 groups within 2 weeks. However, the benefit disappeared in 35% of patients within 6 months of treatment even though 65% of successfully treated subjects had sustained improvement up to this time.

R = Randomized. PC = Placebo control. AC = Active control. VAS = Visual analog scale. SF-36 = Short-form 36 . ODI = Oswestry Disability Index. ODQ = Oswestry Disability Questionnaire . SLR = Straight Leg Raising

Table 8. *Assessment and description of study characteristics of randomized trials and non-randomized studies of fluoroscopically-guided lumbar interlaminar epidurals meeting inclusion criteria.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Manchikanti et al (110,198)	R, AC, F		X		120 with 60 patients in each group	Interlaminar epidural injection with 6 mL of 0.5% preservative-free Xylocaine or 5 mL of 0.5% preservative-free Xylocaine with 6 mg of non-particulate betamethasone.	One year	NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of NRS scores and ODI scores	Significant improvement was demonstrated in 77% of patients in Group I and 67% in Group II. In the successful group, significant improvement was reported in 84% in Group I and 71% in Group II. This is an active control practical trial which fits contemporary interventional pain management practices.
Manchikanti et al (111,199)	R, AC, F	X			120 with 60 patients in each group	Interlaminar epidural injection with 6 mL of 0.5% preservative-free Xylocaine or 5 mL of 0.5% preservative-free Xylocaine with 6 mg of non-particulate betamethasone.	One year	NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of NRS scores and ODI scores	Overall, 67% of patients in Group I without steroids and 85% in Group II with steroids with lumbar disc herniation or radiculitis showed significant improvement. The results were superior and patients were classified with successful response to initial 2 epidural injections (80% vs. 86%).

Table 8 (cont.). *Assessment and description of study characteristics of randomized trials and non-randomized studies of fluoroscopically-guided lumbar interlaminar epidurals meeting inclusion criteria.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Manchikanti et al (147)	R, AC, F			X	60	Interlaminar epidural injection with 6 mL of 0.5% preservative-free Xylocaine or 5 mL of 0.5% preservative-free Xylocaine with 6 mg of non-particulate betamethasone.	One year	NRS, ODI, employment status, opioid intake, significant improvement 50% or greater of NRS scores and ODI scores	Significant pain relief and improvement in ODI scores were seen in both groups at 12 months with 70% in the local anesthetic group and 60% in the steroid group in total patients; whereas, it was 80% in the local anesthetic group and 72% in the steroid group. In this group which successfully responded to the first 2 epidural injections.
Lee et al (165)	R, AC, F	X		X	93	Interlaminar vs. transforaminal.	4 months	NRS, PSI	Transforaminals were better in spinal stenosis than interlaminar epidural - weak evidence.
Rados et al (174)	R, AC, F	X			64	Transforaminal injection of 3 mL of 0.5% Lidocaine and 40 mg of methylprednisolone. Interlaminar with 8 mL of 0.5% Lidocaine with 80 mg of methylprednisolone.	6 months	VAS, ODI	Significant improvements were maintained throughout 6 months of follow-up in both groups.
Kim & Brown (179)	R, AC, F	X			60	Lumbar interlaminar epidural with 80 mg of methylprednisolone or 15 mg of dexamethasone with 2 mL of 0.25% preservative-free Marcaine tand saline (10 mL).	2 to 3 months	VAS, pain medication intake, and emergency room visits	There were no significant differences between dexamethasone and methylprednisolone groups.
Amr (180)	R, AC, F	X			200	Group I received 80 mg of triamcinolone (2 mL), 0.25% bupivacaine 3 mL, plus 30 mg (3 mL of preservative-free ketamine). Group II received 80 mg of triamcinolone (2 mL) and 0.5% bupivacaine (3 mL), plus 3 mL of 0.9% saline.	12 months	Pain scores, Oswestry low back pain disability questionnaire	Authors reported that one week after injection, pain relief was significantly better in Group I compared to Group II and then at all evaluation times. However, both groups showed significant improvement both in short-term and long-term.
Ackerman & Ahmad (181)	R, AC, F	X			90	Caudal versus interlaminar versus transforaminal epidural.	24 weeks	Pain relief	Interlaminar epidural injections were equally effective as caudal but inferior to transforaminal epidural injections.

Table 8 (cont.). *Assessment and description of study characteristics of randomized trials and non-randomized studies of fluoroscopically-guided lumbar interlaminar epidurals meeting inclusion criteria.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Koc et al (194)	R, AC, F			X	29	Group I (n=10) received an inpatient physical therapy program for 2 weeks; Group II (n=10) received 10 mL of solution with 60 mg of triamcinolone acetonide and 3 mL of 0.5% bupivacaine hydrochloride with 5.5 mL of physiologic saline; Group III (n=9) no treatment and served as controls.	6 months	Finger floor distance, treadmill walk test, sit to stand test, weight carrying test, Roland-Morris Disability Index, and Knottingham Health Profile	In this small study, both epidural steroid and physical therapy groups have demonstrated significant improvement in pain and functional parameters and no significant difference was noted between the 2 treatment groups. However, significant improvements were also noted in the control group. Pain and functional assessment scores were significantly more improved in Group II with steroids compared with controls at the second week.
Buttermann (177)	R, AC, F	X			169	Patients were compared with lumbar interlaminar epidural steroid injection with lumbar discectomy. 76% of patients received the injection under fluoroscopic guidance. Fifty patients received epidural injection.	3 years	Pain relief, functional status, neurological status, and pain medication intake	Even though epidural steroid injection was not as effective as discectomy as one would expect, epidural steroid injection did have a role with significant effectiveness for up to 3 years in nearly 50% of the patients who had not had improvement with 6 or more weeks of non-invasive care.
Candido et al (72)	R, AC, F	X			57	Transforaminal vs lateral parasagittal interlaminar.	6 months	Contrast medium spread	Authors concluded that lateral parasagittal interlaminar epidural approach was better than transforaminal epidural approach.
Buttermann (145)	NR, F		X		232 Inflammatory end-plate changes = 93 No inflammatory changes = 139	The injections included either interlaminar or transforaminal utilizing 10 to 15 mg of betamethasone.	2 years	VAS pain scale, pain drawing, Oswestry Disability Index, use of pain medication, and opinion of treatment success	Epidural steroid injections were effective in improving pain and function, as assessed by outcome scores at short-term follow-up. However, at 2 years, less than one-third had not had additional invasive treatment.
Kapural et al (151)	NR, F			X	719	Epidural steroid injection (specifics not available).	12 weeks	VAS, opioid use	Overall, 64% with mild stenosis, 65% with moderate stenosis, and 66% with severe stenosis improved.

Table 8 (cont.). *Assessment and description of study characteristics of randomized trials and non-randomized studies of fluoroscopically-guided lumbar interlaminar epidurals meeting inclusion criteria.*

Manuscript Author(s)	Type of Study	Condition Studied			Number of Patients	Control vs. Intervention or Comparator vs. Treatment	Follow-up Period	Outcome Measures	Results/Comments
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis					
Lee et al (182)	NR, F		X		81	Injection with a mixture of 40 mg of triamcinolone actinide and 15 mL of normal saline and a mixture of 1 mL of 0.5% bupivacaine and 0.5 mL of normal saline with injection of steroid mixture first, followed by the remaining mixture.	One-year	50% relief, NASS satisfaction index	This study included 81 patients in a non-randomized evaluation for effectiveness of axial low back pain with 77.8% showing improvement at short-term follow-up of one month, whereas with a median symptom free interval of 154 days ranging from 96 to 212 days. Thirty-seven percent of the patients reported relief after one-year or longer with 43% reporting approximately 6 months of relief.

R = Randomized. AC = Active control. NR = Non-randomized. F = Fluoroscopy. NRS = Numeric Rating Scale. ODI = Oswestry Disability Index. PSI = Patient Satisfaction Index VAS = Visual Analog Scale. NASS = North American Spine Society

steroid or local anesthetic. Among the active control trials, there were only 2 trials evaluating lidocaine compared with lidocaine with steroid (133,141). The remaining 3 trials were utilizing separate methodology (128,130,136), thus no meta-analysis was possible for non-fluoroscopic studies.

All of the fluoroscopically-guided trials were heterogenous except 2 studies evaluating disc herniation (72,174) assessing the role of transforaminal versus lumbar interlaminar. A total of 8 fluoroscopically-guided randomized trials (72,111,165,174,177,179-181,199) evaluated disc herniation with one duplicate (111,199).

Only one randomized trial evaluated discogenic pain under fluoroscopic guidance (110,198). Three randomized trials evaluated lumbar spinal stenosis under fluoroscopic guidance (147,165,194), whereas 3 studies evaluated without fluoroscopy (141,142,153).

Thus, meta-analysis was not feasible.

2.4 Study Characteristics

The study characteristics of the included studies for both randomized trials and non-randomized studies are illustrated in Table 7 and 8.

2.5 Analysis of Evidence

The evidence was synthesized based on the specific condition for which lumbar interlaminar epidural injection was provided. Table 13 illustrates the results of randomized trials of the effectiveness of lumbar interlaminar epidural injections in managing disc herniation of radiculitis, Table 14 illustrates effectiveness in managing axial or discogenic pain, and Table 15 illustrates effectiveness in managing spinal stenosis.

2.5.1 Disc Herniation and Radiculitis

There were a total of 19 studies meeting the inclusion criteria evaluating lumbar interlaminar epidural injections in managing disc herniation or radiculitis (72,111,128-130,133,135,136,139-142, 144,165, 174,177,179-181,199) with one duplicate (111,199) (Table 13). Among these, 8 randomized trials were performed under fluoroscopy (72,111,165,174,177,179-181,199) with one duplicate (111,199) and11 trials were performed without fluoroscopy (128-130,133,135,136,139-142,144); however, there were no non-randomized evaluations meeting the inclusion criteria. Among the fluoroscopically-guided studies (72,111,165,174,177,179-181,199), there were no placebo controlled evaluations, with all of them being active control trials. Among the studies using a blind

Table 9. *Clinical relevance of included studies.*

Manuscript Author(s)	A) Patient description	B) Description of interventions and treatment settings	C) Clinically relevant outcomes	D) Clinical importance	E) Benefits versus potential harms	Total Criteria Met
FLUOROSCOPICALLY-GUIDED STUDIES						
Candido et al (72)	+	+	+	+	+	5/5
Manchikanti et al (110,198)	+	+	+	+	+	5/5
Manchikanti et al (111,199)	+	+	+	+	+	5/5
Buttermann (145)	+	+	+	+	+	5/5
Manchikanti et al (147)	+	+	+	+	+	5/5
Kapural et al (151)	+	+	+	+	+	5/5
Lee et al (165)	+	-	+	+	-	3/5
Rados et al (174)	+	+	+	+	+	5/5
Buttermann (177)	+	+	+	+	+	5/5
Kim & Brown (179)	+	+	+	+	+	5/5
Amr (180)	+	+	+	+	+	5/5
Ackerman & Ahmad (181)	+	+	+	+	+	5/5
Lee et al (182)	+	+	+	+	+	5/5
Koc et al (194)	+	+	+	+	+	5/5
STUDIES WITHOUT FLUOROSCOPY						
Buchner et al (128)	+	+	+	+	+	5/5
McGregor et al (129)	+	+	-	-	-	2/5
Dilke et al (130)	+	-	+	-	-	2/5
Rogers et al (133)	+	+	+	-	+	4/5
Kraemer et al (135)	+	-	+	-	-	2/5
Pirbudak et al (136)	+	+	+	+	+	5/5
Arden et al (139)	+	+	+	+	+	5/5
Carette et al (140)	+	+	+	-	-	3/5
Cuckler et al (141)	+	+	+	-	-	3/5
Wilson-MacDonald et al (142)	+	+	+	-	-	3/5
Ridley et al (144)	+	+	+	-	-	3/5
Fukasaki et al (153)	+	+	+	+	+	5/5

+ = positive; - = negative ; U = unclear

Scoring adapted from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824 (102).

Table 10. *Methodological quality assessment of fluoroscopically-guided randomized trials.*

	Candido et al (72)	Manchikanti et al (110,198)	Manchikanti et al (111,199)	Manchikanti et al (147)	Lee et al (165)	Rados et al (174)	Buttermann (177)	Kim & Brown (179)	Amr (180)	Ackerman & Ahmad (181)	Koc et al (194)
Randomization adequate	Y	Y	Y	Y	Y	Y	N	Y	Y	N	U
Concealed treatment allocation	N	Y	Y	Y	N	N	N	Y	Y	N	N
Patient blinded	U	Y	Y	Y	N	N	N	Y	Y	N	N
Care provider blinded	N	Y	Y	Y	N	N	N	N	Y	N	N
Outcome assessor blinded	U	N	N	N	N	N	N	N	N	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	N	Y	N	N	N	Y	N
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	U	N	N	N	Y	Y	Y	Y	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	U	Y	Y	Y	N
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	**7/12**	**10/12**	**10/12**	**10/12**	**7/12**	**8/12**	**4/12**	**9/12**	**10/12**	**7/12**	**5/12**

Y=yes; N=no; U=undecided

Table 11. *Methodological quality assessment of blind randomized trials without fluoroscopy.*

	Buchner et al (128)	McGregor et al (129)	Dilke et al (130)	Rogers et al (133)	Kraemer et al (135)	Pirbudak et al (136)	Arden et al (139)	Carette et al (140)	Cuckler et al (141)	Wilson-MacDonald et al (142)	Ridley et al (144)	Fukasaki et al (153)
Randomization adequate	Y	U	U	Y	U	Y	Y	Y	U	Y	Y	Y
Concealed treatment allocation	N	U	U	Y	U	Y	Y	Y	U	Y	U	U
Patient blinded	N	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Care provider blinded	N	N	N	N	U	Y	N	N	N	N	N	N
Outcome assessor blinded	N	N	Y	U	U	U	Y	Y	Y	Y	U	U
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	N	U	Y	U	U	Y	Y	N	Y	Y	Y
Reports of the study free of suggestion of selective outcome reporting	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	N	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Score	**7/12**	**5/12**	**8/12**	**10/12**	**7/12**	**10/12**	**11/12**	**11/12**	**8/12**	**10/12**	**9/12**	**9/12**

Y=yes; N=no; U=undecided

Table 12. *Newcastle-Ottawa quality assessment scale for cohort studies.*

	Buttermann (145)	Kapural et al (151)	Lee et al (182)
Selection			
1) Representativeness of the exposed cohort			
a) truly representative of the average _____ (describe) in the community *	X	X	X
b) somewhat representative of the average pain patients in the community *			
c) selected group of users, e.g. nurses, volunteers			
d) no description of the derivation of the cohort			
2) Selection of the non exposed cohort			
a) drawn from the same community as the exposed cohort *			
b) drawn from a different source	X	X	X
c) no description of the derivation of the non exposed cohort			
3) Ascertainment of exposure			
a) secure record (e.g. surgical records) *	X	X	X
b) structured interview *			
c) written self report			
d) no description			
4) Demonstration that outcome of interest was not present at start of study			
a) yes *			
b) no			
Comparability			
1) Comparability of cohorts on the basis of the design or analysis	X	X	
a) study controls for _____ (select the most important factor) *			
b) study controls for any additional factor * (This criteria could be modified to indicate specific control for a second important factor.)			
Outcome (Exposure)			
1) Assessment of outcome			
a) independent blind assessment *			
b) record linkage *	X	X	X
c) self report			
d) no description			
2) Was follow-up long enough for outcomes to occur			
a) yes (select an adequate follow-up period for outcome of interest) *	X	X	X
b) no			
3) Adequacy of follow-up of cohorts			
a) complete follow-up - all subjects accounted for *	X	X	X
b) subjects lost to follow-up unlikely to introduce bias - small number lost - > _____ % (select an adequate %) follow-up, or description provided of those lost) *			
c) follow-up rate < _____% (select an adequate %) and no description of those lost			
d) no statement			
SCORE	**7/13**	**7/13**	**6/13**

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome categories. A maximum of two stars can be given for comparability.Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (103).

technique without fluoroscopy, 5 were placebo controlled (130,135,139,140,144). Placebo control was inappropriate in some studies and importantly most widely quoted Carette et al's study (140). Dilke et al (130), Arden et al (139), and Ridley et al (144) used appropriate placebo controlled designs either with interspinous injection or intramuscular injection of saline. Others utilized epidural saline, which may not be appropriate, intramuscular steroid injections, or local anesthetic and considered them as placebo controlled. Among the fluoroscopically-guided studies, 2 studies utilized a total of 100 or more patients (111,180,199). Further, only one study (111,199) was carried out utilizing a randomized, active controlled design, providing treatments as needed based on a robust measure of significant improvement considered as 50% improvement in pain and function with 120 patients with one-year follow-up with the number of injections ranging from 1 to 5, with significantly better results in the successful group, and performed in contemporary interventional pain management settings. The second study (180) included 200 patients; however, they compared 80 mg of triamcinolone with 30 mg of preservative-free ketamine or 3 mL of 0.9% sodium chloride solution, illustrating significant improvement in both groups. Among the non-fluoroscopic evaluations, there were 4 studies with more than 100 patients undergoing interventions (130,135,139,140).

Based on the evaluations separating fluoroscopically-guided versus non-fluoroscopic evaluations, results were positive for short-term relief in 5 trials performed under fluoroscopy (111,165,174,180,181,199); whereas, they were undetermined or not applicable in 3 trials (72,177,179). Consequently all of the trials were positive on a short-term basis. Among the trials evaluating long-term relief, there were 4 trials evaluating relief of 6 months or longer (111,174,180,181) and 2 trials evaluating outcomes for longer than one year (111,180). Among these, 4 trials showed positive results (111,174,180,181); whereas, in 2 trials the results were undetermined or not applicable (177,179). Among the studies evaluating at least a one year follow-up, 2 trials showed positive results (111,180); whereas, 2 trials showed the results which were undetermined or not applicable (177,179).

However, with blind randomized trials, the results were highly mixed due to various issues involved. Some of the issues related to providing only one injection or providing injections of 3 in a series and following through a one-year follow-up. With one injection, one could expect relief of 3 to 4 weeks, however, no more than 3 months. Thus, the follow-up after that does not indicate improvement except for the rare patients who show long-term relief. Some of the studies also had flawed selection criteria. Overall, of 11 randomized trials, 7 of them showed short-term positive results (128,130,133,135,136,142,144) and the remaining 4 showed either undetermined or negative results (129,139-141). However, the results were uniformly negative after 3 months or not able to be determined in all the studies except one (136), which showed positive results comparing prednisone with local anesthetic with or without amitriptyline.

2.5.1.1 Effectiveness

Of the 8 randomized trials meeting the inclusion criteria performed under fluoroscopy (72,111,165,174,177,179-181,199), 4 trials showed positive results for short-term relief (111,165,174,180,181,199) with one duplicate (111,199); whereas, in 2 trials, the results were indeterminate or not applicable (177,179). Among the non-fluoroscopic studies, all but one study (136) were negative for long-term relief.

2.5.2 Axial or Lumbar Discogenic Pain

Results are illustrated in Table 14. There were 3 studies meeting the inclusion criteria (110,145,182,198) with one duplicate (110,198). Only one study was randomized, active controlled performed under fluoroscopy (110,198) including 120 patients with one year follow-up showing positive results, both with local anesthetic and steroids performed in a contemporary interventional pain management practice. The other 2 studies (145,182) were non-randomized; however, they were performed under fluoroscopy. There were no placebo-controlled trials evaluating axial or discogenic pain. The only randomized trial also excluded facet joint or sacroiliac joint pain prior to epidural injections and effectiveness (110,198). This trial showed positive results with 60 patients in both groups after exclusion of facet joint or sacroiliac joint pain. This was a large trial in a contemporary interventional pain management practice with an active controlled design showing positive results. Among the 2 non-randomized trials, one study (182) showed positive results at 3 and 6 months; however, the results were unable to be determined at 12 months due to the injections being performed one to 3 not based on return of pain. In the second non-randomized study (145), the results were confusing; thus,

Table 13. *Results of randomized studies of effectiveness of lumbar interlaminar epidural injections in managing disc herniation or radiculitis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment
					3 mos.	6 mos.	12 mos.	Short-term ≤ 6 mos.			Long-term						
											> 6 mos.			1 year			
								ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
Manchikanti et al (111,199)	R, AC, F	10/12	Total = 120 Local anesthetic = 60 Local anesthetic and steroids = 60	Xylocaine or Xylocaine with non-particulate Celestone Number of injections = 1 to 5	72% vs. 82%	63% vs. 85%	67% vs. 85% or 80% vs. 86% in successful group	P	P	NA	P	P	NA	P	P	NA	Positive randomized trial
Lee et al (165)	R, AC, F	7/12	Total = 93 IL = 34 TF = 59	Lidocaine with triamcinolone Number of injections = 1 to 3	SI in both groups	SI in both groups	SI in both groups	P	NA	NA	NA	NA	NA	NA	NA	NA	Positive randomized trial
Rados et al (174)	R, AC, F	8/12	Total = 64 IL = 32 TF = 32	Lidocaine with methylprednisolone Number of injections = 1 to 3	53% vs. 63%	53% vs. 63%	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Short follow-up period
Buttermann (177)	R, AC, F	4/12	Total = 169 Epidural = 38 Discectomy = 119	Local anesthetic and steroids Number of injections = 1	U	U	U	U	U	U	U	U	U	U	U	U	Small, low-quality study
Kim & Brown (179)	R, AC, F	9/12	Total = 60 Depo-Medrol = 30 Dexamethasone = 30	Methylprednisolone or dexamethasone with bupivacaine Number of injections = 1 to 2	NA	NA	U	NA	NA	NA	NA	NA	NA	NA	NA	NA	Relatively small study, with active-control design
Amr (180)	R, AC, F	10/12	Total = 200 Steroid = 100 Steroid + Ketamine = 100	Triamcinolone plus preservative free ketamine and 0.9% saline Number of injections = 1	SI in ketamine group	SI in ketamine group	SI in ketamine group	N	P*	NA	N	P*	NA	N	P*	NA	Significant improvement in both groups, with steroids with or without ketamine
Buchner et al (128)	R, B, AC	7/12	Total = 36 Methylprednisolone group = 17 Control group = 19	Rehabilitation program vs. epidural injections with methylprednisolone and bupivacaine Number of injections = 3 in 14 days	P	P	NA	P	N	NA	P	N	NA	NA	NA	NA	A small study comparing rehabilitation to epidural injections.
McGregor et al (129)	R, B, AC	5/12	Total = 44 Caudal = 22 Lumbar = 22	Bupivacaine with hydrocortisone in saline Number of injections = 1	NSI	NSI	NA	N	NA	N	N	NA	N	NA	NA	NA	Low quality study in a small number of patients without fluoroscopy

Table 13 (cont.). *Results of randomized studies of effectiveness of lumbar interlaminar epidural injections in managing disc herniation or radiculitis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment
					3 mos.	6 mos.	12 mos.	Short-term ≤ 6 mos.			Long-term						
											> 6 mos.			1 year			
								ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
Dilke et al (130)	R, B, PC	8/12	Total = 100 Epidural = 50 Interspinous = 50	Methylprednisolone in normal saline or interspinous ligament Number of injections = 1-2	P	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Placebo control trial with positive responses
Rogers et al (133)	R, B, AC	10/12	Total = 30 Steroid epidural = 15 Non-steroid epidural = 15	Lignocaine with or without methylprednisolone Number of injections = 1	P	NA	NA	P	P	NA	NA	NA	NA	NA	NA	NA	A small prospective single blind study
Candido et al (72)	R, AC, F	7/12	Total = 57 Parasagittal interlaminar = 29 Transforaminal =28	Number of injections = 1-3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Small study
Ackerman & Ahmad (181)	R, AC, F	7/12	Total = 90 Caudal = 30 Interlaminar = 30 Transforaminal = 30	Steroid and saline with local anesthetic. Number of injections = 1 to 3	P	P	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Positive results.
Kraemer et al (135)	R, B, PC, AC	7/12	Total = 133 Perineal = 47 Epidural = 40 Intramuscular = 46	Triamcinolone and local anesthetic Number of injections = 3	68% vs. 53.3% vs. 34.8%	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Positive results.
Pirbudak et al (136)	R, B, AC	10/12	Total = 92 Epidural = 46 Epidural + amitriptyline = 46	Betamethasone and bupivacaine or with addition of amitriptyline Number of injections = 1 to 3	SI in both groups	SI in both groups	SI in both groups	P	P**	NA	P	**	NA	P	P**	NA	Active control trial with positive results
Arden et al (139)	R, B, PC	11/12	Total = 228 Steroid group = 120 Placebo group = 108	Triamcinolone and bupivacaine or normal saline into interspinous ligament Number of injections = 3	NSI	NSI	NSI	N	NA	N	N	NA	N	N	NA	N	Negative results with transient relief in steroid group with multiple deficiencies

Table 13 (cont.). *Results of randomized studies of effectiveness of lumbar interlaminar epidural injections in managing disc herniation or radiculitis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment
					3 mos.	6 mos.	12 mos.	Short-term ≤ 6 mos.			Long-term						
											> 6 mos.			1 year			
								ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
Carette et al (140)	R, B, PC	11/12	Total = 158 Methylprednisolone = 78 Placebo 80	Normal saline vs. depo methylprednisolone and procaine Number of injections = 1 to 3	NSI	NSI	NSI	N	NA	N	N	NA	N	N	NA	N	Inappropriate blind placebo trial with negative results.
Cuckler et al (141)	R, B, AC	8/12	Total = 36 Steroid group = 22 Local anesthetic group - 14	Procaine or methylprednisolone acetate combined with procaine. Number of injections = 1 to 2	NSI	NSI	NSI	N	N	NA	N	N	NA	N	N	NA	A small study without fluoroscopy in acute disc herniation
Wilson-MacDonald et al (142)	R, B, AC	10/12	Total = 60 Intramuscular = 34 Epidural = 26	Intramuscular injection or epidural bupivacaine with methylprednisolone Number of injections = 1 to 2	SI in the treatment group	U	U	P	NA	NA	U	NA	NA	U	NA	NA	Small study
Ridley et al (144)	R, B, PC	9/12	Total = 35 Active group = 19 Placebo group = 16	Interspinous saline vs. epidural methylprednisolone and physiological saline Number of injections = 1	SI	U	U	P	NA	NA	U	NA	NA	U	NA	NA	A small study without injection of local anesthetic

* = ketamine group
** = amitriptyline

R = Randomized; PC = Placebo control; AC = Active-control; F = fluoroscopy; B = blind; IL = interlaminar; TF = transforaminal; ST = steroid; LA = local anesthetic; SAL = saline; SI = Significant improvement; NSI – No significant improvement; P = positive; N = negative; NA = not applicable; U = unclear

Table 14. *Results of randomized and observational studies of effectiveness of lumbar interlaminar epidural injections in managing discogenic or axial pain without disc herniation, radiculitis, facet joint pain or SI joint pain.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results								Comments
								Short-term ≤ 6 mos.			Long-Term					
											> 6 mos			≥ 1 year		
					3 mos.	6 mos.	12 mos	ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
RANDOMIZED																	
Manchikanti et al (110,198)	R, AC, F	10/12	Total = 120 Local anesthetics = 60 Local anesthetics and steroids = 60	Lidocaine alone or with Celestone Number of injections = 1 to 5	83% vs. 73%	72% vs. 75%	77% vs. 67%	P	P	NA	P	P	NA	P	P	NA	Positive results in a large active control trial
NON-RANDOMIZED																	
Buttermann (145)	NR, F	7/13	Epidural patients = not known	Betamethasone Number of injections = 1-2	U	U	U	U	NA	NA	U	NA	NA	U	NA	NA	Confusing design with inaccurate therapy.
Lee et al (182)	NR, F	6/13	Total = 81	Triamcinolone with saline and bupivacaine Number of injections = 1 to 3	78%	77.5%	U	P	NA	NA	P	NA	NA	U	NA	NA	Positive results

R = Randomized; AC = Active-control; NR = Non-randomized; F = Fluoroscopy; ST = Steroid; LA = Local anesthetic; SAL = Saline; P = Positive; N = Negative; NA = Not applicable; U = Unclear

they were classified as undetermined.

2.5.2.1 Effectiveness

Of the one randomized trial (110,198) and 2 non-randomized studies (145,182) the randomized trial and one non-randomized study showed positive results for both short-term and long-term. The third study which was non-randomized (145) showed undetermined results with a confusing design. Only one study evaluated the patients at 12 months with 120 patients (110,198). This study was positive both in short-term and long-term.

2.5.3 Spinal Stenosis

Table 15 shows results of randomized and observational studies of effectiveness of lumbar epidural injections in managing spinal stenosis.

There were 6 randomized trials (141,142,147,155,165,194) and one non-randomized study (151) evaluating the effectiveness of lumbar interlaminar epidural injections in spinal stenosis. However, none of the well-conducted studies utilized 100 or more patients. There were 3 randomized trials performed under fluoroscopy (147,165,194). The study by Manchikanti et al (147) was a preliminary report showing positive results with local anesthetic as well as steroids for central stenosis in a contemporary interventional pain management practice. The other 2 fluoroscopically-guided trials (165,194) and one non-randomized study (151) showed short-term positive results. On a long-term basis, the results were also positive for 6 months or longer in 2 studies (147,194). However, the results were mixed in the groups using a blind technique. One study (142) utilized the intermuscular injection for control with steroids and considered it also as a placebo. Short-term results were positive with blind epidural for spinal stenosis with a small number of patients in one trial (142).

2.5.3.1 Effectiveness

There were 3 randomized trials

(147,165,194) evaluating spinal stenosis under fluoroscopy with all 3 of them showing positive results. However, only one study by Manchikanti et al (147) evaluated long-term follow-up with positive results. The non-randomized trial also performed under fluoroscopy (151) was positive in short-term.

Among the randomized trials, only the study with a small number of patients by Wilson-McDonald et al (142) was positive for short-term relief.

2.6 Level of Evidence

Based on the USPSTF criteria, the evidence is considered at 3 levels – good, fair, or limited.

2.6.1 Lumbar Disc Herniation

For lumbar disc herniation with radiculitis, based on 5 of 8 positive randomized trials performed under fluoroscopy the evidence is good for short-term and long-term relief with steroids and fair with local anesthetic.

Considering the blind trials without fluoroscopy, the evidence continues to be good for short-term relief with positive results in 7 of the 11 studies with local anesthetic and steroids. However, the level of evidence based only on the 4 trials showing negative or undetermined results some of which are placebo controlled, is poor to fair. Similarly, for long-term relief, the results in the majority of the studies were negative or undetermined with positive results in only one trial with poor evidence.

Overall, results are positive with good evidence when performed utilizing contemporary interventional pain management techniques with measures of pain and function and repeating them only based on the return of pain with local anesthetic and steroids; however, the evidence is fair when they are performed with only local anesthetic.

2.6.2 Axial or Lumbar Discogenic Pain

For axial or lumbar discogenic pain, based on one of one positive randomized trial (110,198) performed under fluoroscopy, the evidence is considered fair for short-term and long-term relief with steroids or with local anesthetic.

2.6.3 Spinal Stenosis

For spinal stenosis, based on 3 of 3 positive randomized trials and one positive non-randomized study performed under fluoroscopy, the evidence is considered fair for short-term and long-term relief with local anesthetic and steroids.

2.6.4 Summary of Evidence

In summary, the evidence is good for radiculitis secondary to disc herniation with local anesthetics and steroids, fair with local anesthetic only; whereas, it is fair secondary to spinal stenosis with local anesthetic and steroids, and fair for axial pain without disc herniation and with local anesthetic with or without steroids.

3.0 Complications

The commonly described complications of interlaminar epidural injections are related either to the needle placement or drug administration (1,46,47,50-59). Multiple infectious complications including epidural abscess, meningitis, and osteomyelitis/discitis have been reported (200-209). One potentially serious complication of the epidural injection is epidural hematomas in patients with or without evidence of any bleeding tendency, anticoagulation, or traumatic needle insertion (210-216). Neurological injuries, though rare, could be devastating related to needle trauma, intraarticular injection, toxic effects of steroids, bleeding, and infection (74,200-227). Other complications include increased pain, seizures, chemical meningitis, dural puncture, disc puncture, subdural air, pneumocephalus, transient blindness, retinal necrosis, chorioretinopathy, hiccups, flushing, and arterial gas embolism (200,228-245). The major theoretical complications of corticosteroid administration include suppression of pituitary adrenal axis, hypercorticism, Cushing's syndrome, osteoporosis, avascular necrosis of the bone, steroid myopathy, epidural lipomatosis, weight gain, fluid retention, and hyperglycemia (206,217,218,246-251).

Manchikanti et al (251) in evaluating 10,000 fluoroscopically-guided epidural injections showed intravascular and return of blood in 0.5%, profuse bleeding and dural puncture in 0.8%, local hematoma and transient nerve root irritation in 0.28%, postlumbar puncture headache in 0.07%, and facial flushing in 0.13% in lumbar interlaminar epidural injections.

Finally, radiation exposure is also a potential problem with damage to eyes, skin, and gonads (252-254).

4.0 Discussion

This systematic review of fluoroscopically-guided and blind lumbar interlaminar epidural injections in managing chronic low back pain and lower extremity pain of disc herniation or radiculitis indicated good evidence for procedures performed under fluoroscopy.

Table 15. *Results of randomized and observational studies of effectiveness of lumbar interlaminar epidural injections in managing spinal stenosis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comments
					3 mos.	6 mos.	12 mos	Short-term ≤ 6 mos.			Long-Term						
											> 6 mos			≥ 1 year			
								ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
RANDOMIZED																	
Manchikanti et al (147)	R, AC, F	10/12	Total = 60 Local anesthetic = 30 Local anesthetic and steroids = 30	Local anesthetic or local anesthetic with non-particulate Celestone. Number of injections = 1 to 5	77% vs. 63%	67% vs. 67%	70% vs. 60%	P	P	NA	P	P	NA	P	P	NA	The first randomized controlled study with long-term follow-up
Lee et al (165)	R, AC, F	7/12	Total = 99 IL = 42 Bilateral TF = 57	Lidocaine and triamcinolone Number of injections = 1 to 3	SI in both groups	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Short-term follow-up
Koc et al (194)	R, AC, F	5/12	Total = 29 Inpatient physical therapy = 10 Epidural steroid injection = 10 No treatment = 9	Physical therapy program or epidural injection triamcinolone and bupivacaine Number of injections = 1	SI in both groups vs. control	SI in both groups vs. control	NA	P	NA	NA	P	NA	NA	NA	NA	NA	A very small study with positive results
Fukasaki et al (153)	R, B, AC, PC	9/12	Total = 53 Epidural saline = 16 Mepivacaine = 18 Mepivacaine and methylprednisolone = 19	Saline or mepivacaine ora combination of mepivacaine and methylprednisolone Number of injections = 1-3	12.5% vs. 55.5% vs. 63.2%	NA	NA	P	P	N	NA	NA	NA	NA	NA	NA	A small study with 3 groups
Cuckler et al (141)	R, B, AC	8/12	Total = 37 Steroid group = 20 Local anesthetic group - 17	Procaine with or without methylprednisolone Number of injections = 1 to 2	NSI	NSI	NSI	N	N	NA	N	N	NA	N	N	NA	A small study without fluoroscopy
Wilson-MacDonald et al (142)	R, B, AC	10/12	Total = 50 Epidural = 21 Intramuscular injection (control) = 29	Intramuscular injection in the epidural area or epidural with bupivacaine or methylprednisolone Number of injections = 1	SI in treatment group	U	U	P	NA	NA	U	NA	NA	U	NA	NA	A small study without fluoroscopy
NON-RANDOMIZED																	
Kapural et al (151)	NR, F	7/13	Total = 719	Epidural steroid injection Number of injections = 1 to 3	P	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Retrospective evaluation

R = Randomized; AC = Active-control; NR = Non-randomized; PC = Placebo controlled; B = Blind; F = Fluoroscopy; ST = Steroid; LA = Local anesthetic; SAL = Saline; P = Positive; N = Negative; NA = Not applicable; U = Unclear; SI = Significant improvement; NSI = No significant improvement

The evidence is fair for spinal stenosis and discogenic or axial pain due to a paucity of literature. We have not evaluated the evidence for lumbar postlaminectomy syndrome as this is not a commonly performed procedure and is considered unsafe with an interlaminar approach. However, for blind lumbar epidural injections the evidence is highly variable and consistently inferior to fluoroscopically-guided epidural injections with local anesthetic and steroids; and evidence is fair for local anesthetic only.

Thus, in addition to the paucity of available fluoroscopic literature meeting inclusion criteria, all of the included non-fluoroscopic studies followed flawed methodology without target delivery of steroids, performing the procedures frequently between L3/4 and occasionally L4/5 in the lateral position, with poor assessment of outcomes application and analysis. The disadvantages of this approach without fluoroscopy include dilution of the injectate, extra epidural placement of the needle, intravascular placement of the needle, preferential cranial flow of the solution, preferential posterior flow of the solution, difficult placement (with increased risks in postsurgical patients), difficult placement below L4-L5 interspace, deviation of needle to non-dependent side, dural puncture, and trauma to the spinal cord. These disadvantages and potential flaws may be avoided with fluoroscopy.

The ultimate results of this systematic review are in stark contrast to previous systematic reviews and guidelines. However, in this evaluation we attempted to evaluate the evidence separately for procedures performed under fluoroscopy for disc herniation and radiculitis, spinal stenosis, and chronic axial or discogenic pain; whereas, others have evaluated by combining multiple conditions and multiple techniques (caudal and interlaminar), fluoroscopically-guided and non-fluoroscopic into one category.

The evidence here is similar compared to caudal epidurals or transforaminal epidurals with or without steroids. Further, when the injections were performed under fluoroscopy, interlaminar epidurals, similar to caudal epidurals, showed superior results in all conditions, including axial or discogenic pain without disc herniation and spinal stenosis.

The debate concerning lumbar epidural steroid injections has been nurtured since the 1970s (1,15,20,26,46,48,49,51-53,56,59,96,102,255). The first systematic review of the effectiveness of caudal epidural steroid injections was performed by Kepes and Duncalf in 1985 (51). They concluded that the rationale for epidural and systematic steroids was not proven. However, in 1986, Benzon (59), utilizing the same studies, concluded that mechanical causes of low back pain, especially those accompanied by signs of nerve root irritation, may respond to epidural steroid injections.This illustrates that systematic reviews have provided different results based on the evaluators.

Bogduk et al (26) extensively studied caudal, interlaminar, and transforaminal epidural injections, including all the literature available at the time, and concluded that the balance of published evidence supports the therapeutic use of caudal epidurals. In 1995, Koes et al (52) reviewed 12 trials of lumbar and caudal epidural steroid injections and reported positive results from only 6 studies. However, review of their analysis showed that there were 5 studies for caudal epidural steroid injections and 7 studies for lumbar epidural steroid injections. Four of the 5 studies involving caudal epidural steroid injections were positive; whereas, 5 of 7 studies for lumbar interlaminar were negative. Their updated analysis (53) with the inclusion of 15 trials also arrived at the same conclusions with inappropriate allocation of the procedures. Multiple other investigators (52,56,102) also have provided differing conclusions. In general, criticism against systematic reviews in the past has been directed toward methodology, small size of the study populations, and other limitations, including long-term follow-up and outcome parameters of the available literature. Further, the paucity of literature has been a factor in the systematic evaluation of evidence for the effectiveness of epidural injections (15,19,20,27,28,102).

Target site concentration of the administered drug including steroids depends on multiple injection variables including the route of administration. Interlaminar epidural injections are considered to be non-specific. Steroids may be prevented from migrating from the posterior epidural space to the anterior or ventral epidural space by the presence of epidural ligaments or scar tissue, with interlaminar administration. The extra epidural placement of the needle, which may go unrecognized without fluoroscopic guidance, is of paramount importance with the interlaminar approach (61,63,66,67,68,256-260). Other disadvantages of the interlaminar approach include erroneous placement of the needle, which may miss the targeted interspace without fluoroscopic guidance; preferential cranial flow of the solution in the epidural space; deviation of the needle to the non-dependent side; difficulty entering the epidural space and delivery of injectate below

L5, for S1 nerve root involvement; potential risk of dural puncture and post lumbar puncture headache; and finally, the rare, but serious, risk of spinal cord trauma (66,63,66,67,68,256-260). It is a well-known fact that disc herniation mostly involves L4-L5 and L5- S1 discs and the preferential flow to higher levels by placing the needle at L3-4 obviates the entire philosophy of target delivery. Advocates of fluoroscopic guidance point to several studies which have shown that in as many as 30% of the lumbar epidural injections by experienced injectionists, the epidural space was misidentified (66,67,73,256-259). In fact, Botwin et al (73) in their prospective evaluation of epidurography contrast patterns in fluoroscopically-guided lumbar interlaminar epidural injections found that dorsal contrast spread occurred in all patients, whereas ventral spread was present in only 36% of the patients. In addition, they also showed that the mean number of vertebral levels of cephalad spread was 1.28 and caudal spread was 0.88. In another study (61), the spread was unilateral 45% of the time and the contrast spread was anterior only 43% to 51% of the time based on the needle position, indicating over 49% of the time it was posterior.

In this evaluation, a total of 11 randomized trials and 3 non-randomized studies under fluoroscopy were included. However, randomized blind studies were also included. Only the studies meeting at least moderate quality criteria were included in analysis. The quality assessment of all the manuscripts was performed. This review yielded results different from Parr et al (46) published in 2009, the critical review of APS guidelines (28), and the reassessment of the American College of Occupational and Environmental Medicine (ACOEM) guidelines (49). However, these results still do not correlate with results by Chou and Huffman (20) and Staal et al (15,102). Further, results provided by other reviewers are also in line with the evidence from this review (85,255,261).

Peterson and Hodler (261) in their evaluation of evidence-based radiology, evaluating the evidence for use of therapeutic injections for the spine and sacroiliac joints, concluded that caudal epidural steroid injections were superior. Further, the guidelines for the American Society of Anesthesiologists (ASA) and the American Society of Regional Anesthesia in Pain Medicine (ASRA) also provided favorable evidence.

However, Chou and Huffman (20), Staal et al (15,102), ACOEM guidelines (49), and guidelines from American Academy of Neurology (AAN) (56) provided different conclusions. Chou and Huffman (20) in their evaluation stated that most placebo-controlled trials evaluated either the interlaminar or caudal approach. They combined interlaminar or translaminar epidural injections and caudal epidural injections into one category, and therefore reached erroneous conclusions that these treatments were only effective for short-term relief in radiculopathy.

Staal et al (15,102) evaluated all epidural injections in combination which included caudal, lumbar interlaminar, and lumbar transforaminal as one category. They also failed to separate the response to herniation, stenosis, postlaminectomy syndrome, or discogenic pain, consequently reaching inappropriate conclusions. Thus, the present systematic review contradicts this evidence.

ASA and the ASRA guidelines (255), utilizing a combined approach with physician consensus and systematic review, also recommend epidural steroid injections.

The current systematic review shows that lumbar epidural steroid injections, when appropriately performed, should result in significant improvement in pain and function.

Placebo-controlled neural blockade is not realistic. It has been misinterpreted as most placebo solutions injected into active structures result in active effects (140,262-274). The underlying mechanism of action of epidurally administered steroid and local anesthetic injection is still not well understood. It is believed that the achieved neural blockade alters or interrupts nociceptive input, the reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities (1,218). Further, corticosteroids have been shown to reduce inflammation by inhibiting either the synthesis or release of a number of pro-inflammatory mediators and by causing a reversible local anesthetic effect (275-279). Local anesthetics also have been described to provide short- to long-term symptomatic relief based on alteration of various mechanisms including excess nociceptive process, excess release of neurotransmitters, nociceptive sensitization of the nervous system, and phenotype changes (278-285). The prolonged effect of local anesthetics in epidural injections and facet joint nerve blocks has been demonstrated in multiple studies (114-116,119,120,147,284,286-292). Sato et al (293) evaluated the prolonged analgesic effect of epidural bupivacaine in a rat model of neuropathic pain with repetitive administration, possibly by inducing a plastic change in nociceptive input. Further, Tachihara et al (294) showed in rats that nerve root infiltration pre-

vented mechanical allodynia; however, no additional benefit from using corticosteroid was identified.

Further discussions with regards to the superiority of caudal epidurals over either transforaminal epidural injections or interlaminar epidural injections are not proven by this systematic review. This systematic review, however, shows the ability of caudal epidural injections to prevent surgical interventions.

The results of this systematic review may be applied in interventional pain management practices utilizing appropriate evaluations (287). In this systematic review, mostly active-control trials or practical clinical trials were utilized. Practical clinical trials measure effectiveness. Consequently, these are considered more appropriate than explanatory trials meeting efficacy (87,287,295-300). The differences between placebo-control trials and active-control trials include the fact that placebo control trials measure absolute effect size and show the existence of the effect; whereas, active-control trials, not only show the existence of effect, but compared the therapies (256). Thus, the results of this systematic review may be considered generalizable if appropriate selection criteria are utilized.

The limitations of this study include that we were unable to perform meta-analysis for disc herniation, and the paucity of evidence for discogenic pain and spinal stenosis. Further, methodological criteria has been highly variable along with sample sizes. The studies were heterogenous. The results of this systematic review have significant implications for clinical practice. Interlaminar epidural injections show a significant reduction of pain scores in patients with lumbar radiculitis when compared to doing nothing, and conservative management without injection therapy.

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