Systematic Review

Effectiveness of Therapeutic Lumbar Transforaminal Epidural Steroid Injections in Managing Lumbar Spinal Pain

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Background: Among the multiple interventions used in managing chronic spinal pain, lumbar epidural injections have been used extensively to treat lumbar radicular pain. Among caudal, interlaminar, and transforaminal, transforaminal epidural injections have gained rapid and widespread acceptance for the treatment of lumbar and lower extremity pain. The potential advantages of transforaminal over interlaminar and caudal, include targeted delivery of a steroid to the site of pathology, presumably onto an inflamed nerve root. However, there are only a few well-designed, randomized, controlled studies on the effectiveness of steroid injections. Consequently, multiple systematic reviews with diverse opinions have been published.

Study Design: A systematic review of therapeutic transforaminal epidural injection therapy for low back and lower extremity pain.

Objective: To evaluate the effect of therapeutic transforaminal lumbar epidural steroid injections in managing low back and lower extremity pain.

Methods: The available literature on lumbar transforaminal epidural injections in managing chronic low back and 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 by the Newcastle-Ottawa Scale criteria for observational studies. 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.

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

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: For this systematic review, 70 studies were identified. Of these, 43 studies were excluded and a total of 27 studies met inclusion criteria for methodological quality assessment with 15 randomized trials (with 2 duplicate publications) and 10 non-randomized studies.

For lumbar disc herniation, the evidence is good for transforaminal epidural with local anesthetic and steroids, whereas it was fair for local anesthetics alone and the ability of transforaminal epidural injections to prevent surgery. For spinal stenosis, the available evidence is fair for local anesthetic and steroids. The evidence for axial low back pain and post lumbar surgery syndrome is poor, inadequate, limited, or unavailable.

Limitations: The limitations of this systematic review include the paucity of literature.

Conclusion: In summary, the evidence is good for radiculitis secondary to disc herniation with local anesthetics and steroids and fair with local anesthetic only; it is fair for radiculitis secondary to spinal stenosis with local anesthetic and steroids; and limited for axial pain and post surgery syndrome using local anesthetic with or without steroids.

Key words: Spinal pain, chronic low back pain, lower extremity pain, transforaminal epidural steroids, radiculopathy, sciatica, steroids, local anesthetic

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In the United States, epidural injections are one of the most commonly utilized modalities of treatment in managing chronic low back pain and lower extremity pain (1-12). Epidural injections are administered by accessing the lumbar epidural space by multiple routes including transforaminal, caudal, and interlaminar. Substantial differences have been described among these 3 approaches, with the transforaminal approach having the advantage of being target-specific and using the smallest volume, fulfilling the aim of reaching the primary site of pathology, namely the ventral lateral epidural space (2,11,13-17). However, transforaminal epidural injections are also associated with substantial risk compared to either caudal or interlaminar epidural injections (2,8-13,18-29). Further, multiple prognostic indicators (30-33), the depth of the epidural space (34,35), the relationship of the radicular medullary artery (36), injectate volumes required (37-40), filling patterns (14,15), and multiple modifications to improve safety and effectiveness (41-48) are important in treating multiple types of painful conditions (1,7,11,49,50). Transforaminal epidural injections have been utilized for multiple indications including lumbar radiculitis with or without disc herniation, discogenic pain, spinal stenosis, and in post lumbar surgery syndrome (2-5,7,11,51-53). The comparative effectiveness of multiple types of steroids have also been studied (54-56). In addition, utilization of lumbar transforaminal epidural injections has increased 152% for the primary procedure and 218% for subsequent procedures as illustrated from 2002 to 2006 (1,7). From 2000 to 2010, they increased 699% for the primary procedure and 922% for subsequent procedures, an annual increase of 70% and 92%, respectively (57).

Despite increasing utilization of lumbar transforaminal epidural injections, significant debate continues regarding their effectiveness. Buenaventura et al (11), in a systematic review of therapeutic lumbar transforaminal epidural steroid injections, evaluated 4 randomized trials (47,58-60) based on Cochrane musculoskeletal review group criteria, with criteria of short-term relief as < 6 months and long-term relief as > 6 months. They showed Level II-I evidence for short-term relief and Level II-2 for long-term relief in managing chronic low back and lower extremity pain. Chou and Huffman (4) concluded that 3 higher quality, placebo-controlled trials evaluating the transforaminal approach reported mixed results (58-61), and concluded that for low back pain with sciatica, evidence for the efficacy of epidural steroid injection by the transforaminal approach was mixed, with 2 of 3 higher quality trials showing no benefit compared to controlled injections.

In a critical evaluation of American Pain Society (APS) guidelines, Manchikanti et al (62) concluded that the evidence appears to be fair, based on grading of good, fair, and poor in managing lumbar nerve root pain with transforaminal epidural injections. Favorable evidence has also been described in other manuscripts (63-71). Buenaventura et al (11) also showed limited evidence for transforaminal epidural injections for lumbar radicular pain in post surgery syndrome. There were no studies evaluating transforaminal epidural injections in spinal stenosis meeting the inclusion criteria (11). Depalma et al (63) showed that there was moderate evidence in support of selective nerve root blocks in treating painful radicular syndromes. European guidelines (64) for the management of chronic nonspecific low back pain also provided a favorable level of evidence for transforaminal epidural steroid injections, while providing negative evidence for other modalities.

While debate continues, Benny and Azari (68) examined 8 randomized controlled trials (RCTs) (47,58-60,72-75). They showed positive outcomes in both short-term and long-term results, concluding that there was strong evidence for transforaminal injections in the treatment of lumbosacral radicular pain for both short-term and long-term relief. In another evidence-based radiology review (66), the authors concluded that there was moderate to strong evidence supporting the use of transforaminal therapeutic epidural injections for lumbar nerve-root compression. In a systematic review, Roberts et al (65) concluded that there was fair evidence supporting transforaminal epidural injections as superior to placebo for treating radicular symptoms, whereas there was good evidence that they should be used as a surgery-sparing intervention, and that they were superior to interlaminar epidural steroid injections and caudal epidural steroid injections for radicular pain. Rho and Tang (71), in an evaluation of the efficacy of lumbar epidural steroid injections, concluded that there was strong evidence to support the use of lumbar transforaminal epidural steroid injections in patients with acute to subacute unilateral radicular pain caused by a herniated nucleus pulposus or spinal stenosis. They also concluded that a lumbar transforaminal epidural steroid injection is an effective surgery-sparing procedure that should be a part of conservative care in the management of low back pain and radiculopathy.

Quraishi (67), in a recent systematic review and meta-analysis, concluded that when appropriately performed, transforaminal epidural steroid injections should result in an improvement in pain, but not disability. Three RCTs were included that followed patients for 3 months, with results illustrating no benefit by adding steroids.

The objective of this systematic review is to determine the effects of transforaminal epidural injections with or without steroids for various conditions including disc herniation, spinal stenosis, discogenic pain, and post lumbar surgery syndrome. The objectives also include the evaluation of short-term, as well as long-term, pain relief with improvement in functional status.

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 (2,3,76-86), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (87-90), Standards for Reporting Observational Studies (STROBE) (91), Cochrane guidelines (3,81,82), Chou and Huffman's guidelines (4), and quality of reporting of analysis (78).

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 evaluated were lumbar transforaminal epidural injections appropriately performed with proper technique under image 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
   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, post lumbar laminectomy syndrome, spinal stenosis, and radiculitis treated with lumbar transforaminal epidural injections, as well as selective nerve root blocks, and nerve root 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, 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 transforaminal 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 were 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) (80,92). 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.

1.4.4 Methodological Quality or Validity Assessment

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.

The methodological quality assessment was performed in a manner to avoid any discrepancies which were evaluated by a third reviewer and settled by consensus.

The quality of each individual article used in this analysis was assessed by Cochrane review criteria (Table 2) (81) for randomized trials, and Newcastle-Ottawa Scale for observational studies (Tables 3 and 4) (93,94). 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.

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

If there was a conflict of interest with the reviewed manuscript concerning authorship (if the reviewer was also one of the authors) or any other type of conflict,

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 by the practice?			
B) Are the interventions and treatment settings described in sufficient detail to apply its use in clinical practice?			
C) Were all clinically relevant outcomes measured and reported?			
D) Is the size of the effect clinically important?			
E) Do the likely treatment benefits outweigh the potential harms?			

Scoring adapted and modified from Staal JB, et al. Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824 (92).

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 dice (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, 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.	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

Table 2 (cont.). ***Randomized controlled trials quality rating system.***

	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: Furlan AD, Pennick V, Bombardier C, van Tulder Ml; 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 (81)

Table 3. ***Newcastle-Ottawa quality assessment scale: 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 (e.g. 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, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (93).

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, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non-randomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (93).

the involved authors did not review the manuscript for quality assessment.

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 6 of 12 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 7 of the 13 criteria for cohort studies and 5 of 10 for 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 transforaminal epidural injections were also

evaluated separately for disc herniation, discogenic pain, spinal stenosis, and post surgery syndrome.

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 (94). Combined results with I2 > 50% was 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 were 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 (95).

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 (96), chronic musculoskeletal pain (97), and chronic low back pain (76-78,80,83,98,99), which have been commonly utilized. However, recent descriptions of clinically meaningful improvement showed either pain relief or functional status as 50% (100-114). 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 (115).

1.4.9 Software Used for Measurement

The data were analyzed using SPSS Version 9.0.1 statistical software (SPSS Inc., Chicago, IL), Microsoft Access 2003, and Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA) (116).

Meta-analyses were performed with Comprehensive Meta-Analysis Software Version 2.0 for Windows (Biostat Inc., Englewood, NJ) (117).

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

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).
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 US Preventive Services Task Force (4,118).

been utilized by multiple authors (118).

The analysis was conducted using 3 levels of evidence ranging from good, fair, and poor.

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 transforaminal epidural injection therapy was clinically relevant and effective, either with a placebo control or active control. This indicates that the difference in effect for 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, discogenic pain, and post surgery syndrome).

2.0 Results

Figure 1 shows a flow diagram of study selection as recommended by Preferred Reporting Items for System-

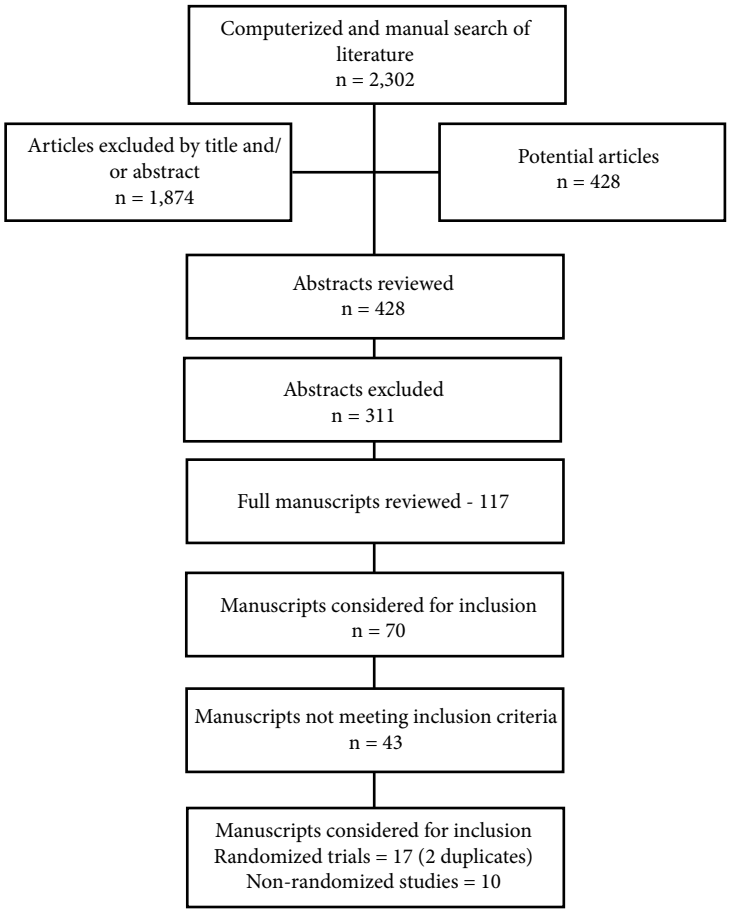

Fig. 1. *Flow diagram illustrating published literature evaluating lumbar transforaminal epidural injections.*

atic Reviews and Meta-Analyses (PRISMA) (79). There were 70 studies considered for inclusion (30,31,40-42,47-49,51-53,58-61,72-75,119-169). The authors of 2 studies were contacted and additional information was obtained (124,158).

Of the 70 lumbar transforaminal epidural trials identified, 43 were excluded (30,40-42,48,49,51,74,75,119,121-123,126,129,130,133,135-143,145,147-150,153,154,157,159-161,164-169). One study (140) was excluded due to an inability to obtain a full manuscript published in 1996 after all attempts had been exhausted. Table 6 shows the reasons for exclusion. Of these, only 10 were randomized trials and 32 were non-randomized studies.

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

Manuscript Author(s)	Condition Studied	Number of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
RANDOMIZED				
Ghahreman & Bogduk (30)	Lumbar radiculitis with disc herniation	71	4 weeks	This is a sub-group analysis of another study published by the same authors.
Park et al (42)	Lumbar intervertebral disc herniations	40 patients with 20 receiving retrodiscal approach and 20 receiving classic approach	8 weeks	Total of only 40 patients with 20 in each group.
Thomas et al (74)	Disc herniation	31	6 days and 30 days	The inclusion criteria was duration of lumbar radiculitis of less than 3 months.
Kraemer et al (75)	Lumbar radicular symptoms	49 patients with 24 and 25 in each group	Unclear	They performed epidural perineural injections blindly and injected either sodium chloride solution or triamcinolone
Kang et al (119)	Lumbar radiculitis secondary to lumbar disc herniation	160	2 weeks	Evaluation of corticosteroid dosage.
Cohen et al (121)	Disc herniation	24	One-month	Patients with subacute lumbosacral radiculopathy of 2 months to one year were studied.
Gallucci et al (138)	Disc herniation	159	6 months	Mean duration of pain was only 15 weeks.
Gharibo et al (157)	Disc herniation	42	4 weeks	A small number of patients were evaluated with short-term follow-up in the acute pain with subacute radiculitis.
Ahadian et al (167)	Disc herniation and spinal stenosis	98	12 weeks	The inclusion criteria was a previously favorable response to transforaminal epidural steroid injections to evaluate the response of epidural dexamethasone.
Ohtori et al (168)	Spinal stenosis	80	one month	The study evaluated the effectiveness of tumor necrosis factor– alpha inhibitor, etanercept, compared with dexamethasone for treatment of sciatica. Inclusion criteria was on average 2.5 months of duration of pain with inclusion of acute or subacute radiculitis.
NON-RANDOMIZED				
Desai et al (40)	Not available	83 from 953	2-4 weeks	Epidural contrast medium flow patterns were evaluated.
Zhu et al (41)	Not applicable	Not applicable	Not applicable	A technical description of an alternative approach.
Kabatas et al (48)	Lumbar spinal stenosis and lumbar discogenic pain with radiculopathy	40	3 months	A retrospective evaluation of 40 patients.

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

Manuscript Author(s)	Condition Studied	Number of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
DeGregoris & Diwan (49)	Phantom radiculitis	One	one year	A single case report.
Smith et al (51)	Symptomatic lumbar spinal stenosis	38	6 weeks	A small retrospective analysis.
Riboud et al (122)	Disc herniation and spinal stenosis	50	6 months	Non-randomized study with inadequate sample size.
Fish et al (123)	Lumbar radiculopathy	39	6 months	The use of electromyelography to predict functional outcome was evaluated.
Karaeminogullari et al (126)	Lumbar radicular pain secondary to spinal stenosis	42	6 months	Small study under computed tomography.
Lee et al (129)	Lumbar radiculitis without previous surgery	108	2 weeks	The temporary diagnostic relief was evaluated.
Schaufele et al (130)	Lumbar disc herniations	20	18.7 days	Small observational report.
Fish et al (133)	Lumbar radiculitis	One	Not available	Technical description.
Botwin et al (135)	Degenerative lumbar spinal stenosis	34	One-year	A small cohort study.
Devulder (136)	Failed back surgery syndrome	20	3 months	A retrospective pilot study with a small number of patients.
Kolsi et al (137)	Disc herniation	30	28 days	Poorly described or translated outcomes, results, and conclusions.
Lee et al (139)	Sciatica	56	2 weeks	A prospective evaluation with a 2 week follow-up.
Tong et al (141)	Disc herniation	76	122 days	The description of the duration of the pain was not provided.
Stalcup et al (142)	Selective lumbar nerve root blocks	1,777	30 minutes	Evaluation of influence of needle-tip position.
Yang et al (143)	Unilateral sciatica	19	24 months	Assessment by questionnaires.
Michel et al (145)	Sacral one level radiculopathy	41	90 days	Small study
Melzer & Seibel (147)	Multiple pain problems secondary to degenerative spinal diseases	161	Unclear	Magnetic resonance guided transforaminal epidurals.
Sequeiros et al (148)	Disc herniation	61	6 months	Magnetic resonance imaging utilization of periradicular nerve root infiltration.
Zennaro et al (149)	Lumbar and sacral radiculitis	41	5 months	A comparison of 2 techniques under computed tomography scanning
Groenemeyer et al (150)	Radicular pain	26	9 months	A CT-guided periradicular injections of corticosteroids.
Marchetti et al (153)	Radiculopathy	89	10 days	Evaluation of outcomes based on electromyelographic findings.
Conliffe et al (154)	Evaluation of herpes zoster radiculopathy	one	Unclear	Only one case of herpes zoster radiculopathy.

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

Manuscript Author(s)	Condition Studied	Number of Patients	Reason for Exclusion	
			Follow-up Period	Other Reason(s)
Kim et al (159)	Intravascular flow patterns of transforaminal epidural injections	182	Not available	Intravascular flow patterns were studied.
Cyteval et al (160)	Disc herniation and spinal stenosis	229	2 weeks	Short-term follow-up with high doses of steroid.
Smuck et al (161)	Contrast dispersal patterns	Unknown	Not applicable	Evaluation of contrast dispersal patterns.
Weiner and Fraser (164)	Disc herniation	30	3.4 years	Small sample size.
Lee et al (165)	Disc herniation	143	3 months	Inclusion of subacute radiculitis
Atim et al (166)	Disc herniation	37	6 months	Small retrospective report
Delport et al (169)	Spinal stenosis	149	Unclear	Confusing data with patients receiving transforaminal, caudal, and combinations.

Table 7 illustrates characteristics of studies considered for inclusion. There were 5 short-term randomized trials (61,72,120,125,152), 10 randomized trials evaluating long-term follow-up (47,52,58-60,73,124,132,134,155,156,162) with 2 duplicate publications (58,59,132,134), 3 non-randomized studies for short-term relief (31,53,144), and 7 long-term non-randomized studies (127,128,131,146,151,158,163). Follow-up of less than 6 months was considered as short-term and 6 months or longer was considered as long-term.

2.1 Clinical Relevance

Of the 25 studies assessed for clinical relevance, 23 studies met criteria with a score of 3 out of 5 or greater (31,47,52,53,58-61,72,73,120,124,125, 127,128,131,144, 151,152,155,158,162,163). Table 8 illustrates the assessment of clinical relevance.

2.2 Methodological Quality Assessment

A methodological quality assessment of the RCTs meeting inclusion criteria was carried out utilizing Cochrane review criteria as shown in Table 9. 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 5 randomized trials evaluating a short-term response of less than 6 months (61,72,120,125,152), with 3 scoring high quality (61,120,152), and 2 scoring moderate quality (72,125).

There were 9 randomized trials (after combining duplicates) evaluating long-term response of 6 months or longer (47,52,58-60,73,124,155,162), with 3 trials considered high quality (47,58,162), 5 trials considered moderate quality (52,59,73,124,155), and one trial considered low quality (60).

A methodological quality assessment of the observational studies meeting inclusion criteria was carried out utilizing Newcastle-Ottawa Scales as illustrated in Tables 10 and 11. 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.

For case-control studies, 8 or higher was considered as high quality, 5 to 7 was considered as moderate quality, and less than 5 was considered low quality and those studies were excluded.

There were 3 non-randomized or observational studies including case reports evaluating short-term effectiveness of transforaminal epidural injections with follow-up of less than 6 months (31,53,144). Of these, 2 were considered moderate quality (53,144), and one was of low quality (31).

There were 7 non-randomized or observational studies, including case reports, evaluating

Table 7. *Assessment of randomized trials and non-randomized studies for 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	Comment(s)
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis	Post Surgery Syndrome					
RANDOMIZED – SHORT-TERM										
Ghahreman et al (120)	R, PC	X				150	Intramuscular injection of normal saline, intramuscular injection of steroid, transforaminal injection of normal saline, local anesthetic, or steroid	One-month	At least 50% pain relief	This study illustrated effectiveness of steroids in comparison with placebo as well as local anesthetic. The study also showed that transforaminal epidural injections were more effective than blindly performed intraspinous steroid injections.
Ng et al (61)	R, AC	X		X**		86	Bupivacaine only 2 mL 0.25% or bupivacaine 0.25% with 40 mg of methylprednisolone	12 weeks	VAS, ODI, change in walking distance, claudication, satisfaction of the outcome	Corticosteroids did not provide additional benefit
Lee et al (72)	R, AC	X*		X*		192	Interlaminar vs. transforaminal	4 months	NRS, PSI	Transforaminals were better in spinal stenosis than interlaminar epidural - weak evidence.
Park et al (125)	R, AC	X				106	Triamcinolone acetate 40 mg versus dexamethasone 7.5 mg administered transforaminally	One-month	VAS, Short MPQ, ODI	Triamcinolone was more effective than dexamethasone.
Burgher et al (152)	R, AC	X				26	Clonidine with local anesthetic, 200 or 400 mcg, vs 40 or 80 mg of triamcinolone with normal saline	One-month	NRS, RMDQ, ODI	The results showed addition of clonidine to local anesthetic yielded better results than triamcinolone with preservative free normal saline.
RANDOMIZED – LONG-TERM										
Karppinen et al (58,134)	R, PC	X				160	Periradicular infiltration of either sodium chloride solution or methylprednisolone and bupivacaine	One-year	VAS, ODI, Nottingham Health Profile, cost, physical examination	At 6 months, the control group had a greater reduction of pain than the treatment group. At one-year follow-up, both groups demonstrated statistically significant improvements compared with status before injections, but there were no differences between groups.
Jeong et al (47)	R, AC	X		X		239	Transforaminal epidural with ganglionic approach or preganglionic approach	6 months to one-year	VAS	The results illustrated better effect with preganglionic approach compared to a ganglionic approach at short-term follow-up.
Gerszten et al (52)	R, AC	X				90	Transforaminal epidural injection versus nucleoplasty	2 years	VAS, SF-36	At one-year follow-up nucleoplasty patients fared better than transforaminal epidural injection patients.

Table 7 (cont.). *Assessment of randomized trials and non-randomized studies for 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	Comment(s)
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis	Post Surgery Syndrome					
Riew et al (59,132)	R, AC	X		X		55	Either 1 mL of 0.25% bupivacaine or 1 mL of 0.25% bupivacaine and 6 mg of betamethasone	5 years	North American Spine Society Outcome Instrument and operative treatment considered as failure of injection treatment	Selective nerve root injections of corticosteroids were significantly more effective than those of bupivacaine alone when obviating the need for a decompression.
Vad et al (60)	R, AC	X				48	Paraspinal trigger point injections of saline versus transforaminal epidural steroid injections of Xylocaine (lidocaine) and betamethasone	16 months	50% pain reduction, RMDQ, satisfaction score	The study strongly suggested that in treating radicular pain caused by herniated nucleus pulposus, transforaminal epidural steroid injections, improve symptoms and patient satisfaction more than trigger points.
Ackerman & Ahmad (73)	R, AC	X				90	Caudal versus interlaminar versus transforaminal epidural, lumbar disc herniation	24 weeks	Pain relief	Transforaminal epidural steroid injections were more effective than caudal or interlaminar routes.
Candido et al (124)	R, AC	X		X		57	Lateral parasagittal interlaminar vs. transforaminal	6 months	Contrast medium spread	Poorly described
Rados et al (155)	R, AC	X				64	Lumbar interlaminar vs. lumbar transforaminal	6 months	VAS scores, ODI, Disability scores	There was no significant difference between both groups when it was performed under fluoroscopic visualization.
Devulder et al (156)	R, AC				X	60	3 groups: Bupivacaine with steroid versus bupivacaine with hyaluronidase versus bupivacaine hyaluronidase with steroid	6 months	Verbal pain rating scale	Differences were found among the 3 groups, however, results were diminished at 3 and 6-month follow-up
Tafazal et al (162)	R, AC	X		X**		150	Transforaminal epidural with either bupivacaine or bupivacaine with methylprednisolone	One-year	VAS, ODI, LBOS, modified somatic perception questionnaire, MZD	Peri-radicular infiltration of corticosteroids for sciatica does not provide any additional benefit when compared to local anesthetic injection alone.

Table 7 (cont.). *Assessment of randomized trials and non-randomized studies for 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	Comment(s)
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis	Post Surgery Syndrome					
NON-RANDOMIZED – SHORT-TERM										
Park & Lee (31)	NR, P			X		55	C-reactive protein	4 weeks	VAS score	Short-term role of C-reactive protein
Lee et al (53)	NR, RE	X		X		233	Interlaminar vs. transforaminal vs. caudal	2 months	VAS, PSI	Higher ratio of successful results were found in interlaminar and transforaminal techniques than caudal technique.
Ng & Sell (144)	NR	X		X		117		3 months	VAS, ODI, MZD, MSPQ	The results showed there was a significantly better response to periradicular infiltration for radicular pain patients with lumbar disc herniation than the spinal stenosis.
NON-RANDOMIZED – LONG-TERM										
Lutz et al (128)	NR, P	X				69	No comparator	80 weeks	75% relief	The results showed 75% of the patients with successful long-term outcome with average injections of 1 to 4.
Berger et al (146)	NR, P	X	X			139	No comparator	14.8 months	> 50% pain relief, medication, satisfaction, function	The results showed significant pain relief which was lasting in 60.7% of the patients.
Cooper et al (127)	NR, RE, CC			X		61	No comparator	2 years	NRS, NASS Scale, pain medication usage, function and pain status assessment	Results showed approximately 60% of the patients showed a successful outcome at one-week post injection, 60% at one-month post injection, 37% at one-year post injection.
Rosenberg et al (131)	NR, RE	X	X	X	X	82	No comparator	12 months	Pain relief	Authors reported greater than 50% pain relief. Authors reported greater than 50% improvement after one-year in 23% of patients with previous back surgery, 59% in patients with disc herniation group, 35% of patients with spinal stenosis, and 67% in patients without MRI findings.
Manchikanti et al (151)	NR, RE, CC	X	X	X	X	225	Blind interlaminar versus fluoroscopically guided caudal versus transforaminal	1 year	Greater than 50% relief, cost-effectiveness	Epidural administration of corticosteroids under fluoroscopy by caudal or transforaminal route was a valuable, safe, and cost-effective technique.

Table 7 (cont.). *Assessment of randomized trials and non-randomized studies for 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	Comment(s)
		Disc herniation or radiculitis	Discogenic pain without disc herniation	Spinal stenosis	Post Surgery Syndrome					
Mendoza-Lattes et al (158)	NR, RE, CC	X				93	Caudal versus transforaminal	Up to 2 years	ODI, VAS, SF-36	Approximately 60% of the patients improved.
Wang et al (163)	NR, RE	X				69	No comparator	12-27 months	The need for surgical interventions	77% (53 of 69) of the patients significantly decreased their symptoms at 12 to 27 months. Only 23% of the patients failed to improve and had surgical treatment.

* = axial pain
** = foraminal
R = Randomized
PC = Placebo control
DR = Dose response
AC = Active control
NR = Non-randomized
P = Prospective
RE = Retrospective
CC = Case control
VAS = Visual analog scale
ODI = Oswestry Disability Index
NRS = Numeric rating scale
PSI = Patient Satisfaction Index
MPQ = McGill Pain Questionnaire
RMDQ = Roland Morris Disability Questionnaire
SF-36 = Short Form-36 Health Survey
MZD = Modified Zung Depression
MSPQ = Modified Somatic Perception Questionnaire
LBOS = Low Back Outcome Score
NASS = North American Spine Society

long-term effectiveness of transforaminal epidural injections with follow-up of 6 months or longer (127,128,131,146,151,158,163). Of these, 2 were considered moderate quality (151,158) and 5 were of low quality (127,128,131,146,163).

Of the included condition-specific studies, 22 studies evaluated or included disc herniation (47,52,53,58-61,72,73,120,124,125,128,131,132,134,144,146,151,152,155,158,162,163), 3 studies included disc-related axial pain without disc herniation or radiculitis (131,146,151), 12 studies included spinal stenosis (31,47,53,59,61,72,124, 127,131,132,144,151,162), and 3 studies included post surgery syndrome (131,151,156).

2.3 Meta-Analysis

All randomized trials were evaluated for homogeneity for inclusion in the meta-analysis. There were no homogeneous studies in the placebo-control group. Among the active control studies, a maximum of 4 trials met homogenous criteria with transforaminal compared to interlaminar. Of these, one was of short-term follow-up (72) and 2 were of long-term follow-up (124,155).

Other short-term studies included one study comparing bupivacaine versus steroid (61), one comparing triamcinolone versus dexamethasone (125) and one comparing clonidine versus steroid (152).

The long-term follow-up studies included bupivacaine versus steroid (59,162), preganglionic versus post ganglionic approach (47), transforaminal versus interlaminar (124,155), transforaminal versus nucleoplasty (52), transforaminal versus trigger points (60), and transforaminal versus interlaminar versus caudal (73).

Consequently, no meta-analysis was feasible.

2.4 Study Characteristics

Tables 12 and 13 illustrate the study characteristics of the included studies for both randomized (47,52,58-61,72,73,120,124,125,132,134,152,155,156,162) and non-randomized studies (31,53,144,151,158).

2.5 Analysis of Evidence

The evidence was synthesized based on the specific condition for which the transforaminal epidural injection was provided. Table 14 illustrates the results of randomized and observational studies of the effectiveness of transforaminal epidural injections in managing disc herniation or radiculitis, whereas Table 15 illustrates effectiveness in managing spinal stenosis.

Table 8. *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
Park & Lee (31)	+	+	+	+	+	5/5
Jeong et al (47)	+	+	+	+	+	5/5
Gerszten et al (52)	+	+	-	-	+	3/5
Lee et al (53)	+	+	-	-	+	3/5
Karppinen et al (58,134)	+	+	+	+	+	5/5
Riew et al (59,132)	+	+	+	+	+	5/5
Vad et al (60)	+	+	+	+	+	5/5
Ng et al (61)	+	+	+	+	+	5/5
Lee et al (72)	+	-	+	+	-	3/5
Ackerman & Ahmad (73)	+	+	+	+	+	5/5
Ghahreman et al (120)	+	+	+	+	+	5/5
Candido et al (124)	+	+	+	+	+	5/5
Park et al (125)	+	+	+	-	+	4/5
Cooper et al (127)	+	+	+	+	+	5/5
Lutz et al (128)	+	+	+	+	+	5/5
Rosenberg et al (131)	+	+	+	+	+	5/5
Ng & Sell (144)	+	+	+	+	+	5/5
Berger et al (146)	+	-	-	-	-	1/5
Manchikanti et al (151)	+	+	+	+	+	5/5
Burgher et al (152)	+	-	-	+	+	3/5
Rados et al (155)	+	+	+	+	+	5/5
Devulder et al (156)	+	-	-	-	-	1/5
Mendoza-Lattes et al (158)	+	+	+	+	+	5/5
Tafazal et al (162)	+	+	+	+	+	5/5
Wang et al (163)	+	-	-	+	+	3/5

+ = positive; - = negative
Scoring adapted and modified from Staal JB, et al. Nelemans P. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824 (92).

2.5.1 Disc Herniation and Radiculitis

There were a total of 22 studies meeting the inclusion criteria evaluating transforaminal epidural injections in managing disc herniation or radiculitis (Table 14). However, one randomized trial (60) and 4 non-randomized studies (128,131,146,163) were of low quality and failed to meet the final inclusion criteria. Thus, 13 randomized trials (47,52,58,59,61,72,73,120, 124,125,152,155,162) and 4 non-randomized studies (53,144,151,158) were included in the final analysis.

There were 2 studies (58,120) evaluating with a placebo control; however, only the study by Ghahreman et al (120) was a true placebo evaluation study with 2 control groups and 3 treatment groups. The second study by Karppinen et al (134) utilized sodium chloride solution transforaminally in patients with subacute radiculopathy. Even then, the study results showed that the differences were significant compared to the baseline; however, there were no differences between the steroid group and the saline group. Thus, the study

Table 9. *Methodological quality assessment of randomized trials.*

	Ghahreman et al (120)	Karppinen et al (58,134)	Riew et al (59,132)	Burgher et al (152)	Jeong et al (47)	Gerszten et al (52)	Vad et al (60)	Lee et al (72)	Ackerman & Ahmad (73)	Ng et al (61)	Candido et al (124)	Park et al (125)	Rados et al (155)	Devulder et al (156)	Tafazal et al (162)
Randomization adequate	Y	Y	U	Y	U	Y	U	Y	N	Y	Y	N	Y	U	Y
Concealed treatment allocation	Y	Y	U	Y	U	N	N	N	N	Y	N	U	N	N	Y
Patient blinded	Y	Y	Y	Y	Y	N	N	N	N	Y	U	Y	N	N	Y
Care provider blinded	Y	Y	N	Y	N	N	N	N	N	N	N	N	N	N	N
Outcome assessor blinded	Y	Y	Y	Y	Y	N	U	N	N	Y	U	U	N	N	N
Drop-out rate described	N	Y	N	Y	Y	Y	N	Y	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	Y	Y	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	Y	Y	Y
Groups similar at baseline regarding most important prognostic indicators	Y	N	Y	Y	Y	N	Y	Y	Y	N	U	Y	Y	U	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	U	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	Y	Y	Y
Score	11/12	11/12	8/12	12/12	9/12	7/12	5/12	7/12	7/12	10/12	7/12	8/12	8/12	6/12	10/12

Y=yes; N=no; U=unclear

Table 10. *Methodological quality assessment of case control studies.*

	Manchikanti et al (151)	Lee et al (53)	Mendoza-Lattes et al (158)
Selection			
1) Is the case definition adequate?			
a) yes, with independent validation *	X	X	X
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 *	X	X	X
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.) *	X	X	X
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) *	X	X	X
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 *	X	X	X
b) no			
3) Non-Response rate			
a) same rate for both groups *	X	X	X
b) non respondents described			
c) rate different and no designation			
SCORE	6/10	6/10	6/10

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, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (93).

Table 11. *Methodological quality assessment of cohort studies.*

	Lutz et al (128)	Rosenberg et al (131)	Berger et al (146)	Park and Lee (31)	Ng and Sell (144)	Cooper et al (127)	Wang et al (163)
Selection							
1) Representativeness of the exposed cohort							
a) truly representative of the average _____ (describe) in the community *	X	X	X	X	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							
c) no description of the derivation of the non exposed cohort							
3) Ascertainment of exposure							
a) secure record (eg surgical records) *		X	X	X	X	X	X
b) structured interview *	X						
c) written self report							
d) no description							
4) Demonstration that outcome of interest was not present at start of study							
a) yes *	X	X	X	X	X	X	X
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.)					X		
Outcome (Exposure)							
1) Assessment of outcome							
a) independent blind assessment *							
b) record linkage	X	X	X	X	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	X	X	X	X
b) no							
3) Adequacy of follow up of cohorts							
a) complete follow up - all subjects accounted for *	X	X	X	X	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	**6/13**	**6/13**	**6/13**	**5/13**	**7/13**	**6/13**	**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, Shea B, O'Connell D, Peterson J, Welch V, Losos M, Tugwell P. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (93).

Table 12. *Transforaminal epidural steroid injections either with placebo or active control.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths\ Weaknesses	Methodological Quality Assessment Score
Ghahreman et al, 2010 (120)	150 patients who had pain radiating in the lower limb with a positive SLR and a disc herniation confirmed by (CT or MRI.	The patients were then randomized into receiving a fluoroscopically guided lumbar transforaminal injection of a steroid (triamcinolone), a local anesthetic (bupivacaine) or saline versus a placebo intramuscular injection of steroid or saline.	The control groups received an intramuscular injection of normal saline or steroid. Treatment groups received a transforaminal injection of steroids, transforaminal injection of normal saline, or transforaminal injection of local anesthetic. Number of injections=1 to 3	The primary outcome measure was the proportion of patients who obtained complete relief or at least 50% relief of pain for at least one-month after treatment.	One week for all and patients with continuing relief were assessed at 3, 6, and 12 months, or until relief of pain ceased.	Results demonstrated that there was a significantly greater proportion of patients treated with a TFESI (54%) who achieved relief of pain when compared with patients treated with TFI of local anesthetic (7%) or saline (19%) or intramuscular injections of steroids (21%) or saline (13%). Relief of pain was accompanied by significant improvements in function and disability. Over time, the relief of pain diminished in all groups equally.	Strengths Excellent study design with a true placebo for the first time in the history of randomized double-blind placebo controlled trials. Weaknesses All patients were not followed uniformly resulting in a very short period of follow-up for some patients.	12/12
Karppinen et al, 2001 (58,134)	160 patients with sciatica who had unilateral symptoms of one to 6 months duration who never underwent surgery.	Patients were randomly assigned to receive periradicular infiltration either with methylprednisolone-bupivacaine or saline.	Periradicular infiltration of either sodium chloride solution, or methylprednisolone and bupivacaine, 2-3 mL volume per level. Number of injections=1	VAS, ODI, Nottingham Health Profile, cost, physical examination.	One year	At 6 months, the control group had a greater reduction in both back and leg pain than the treatment group. At one-year follow-up, both groups demonstrated statistically significant improvements compared with their status before injections, but there were no differences between groups.	Strengths At 6 months, the control group had a greater reduction in both back and leg pain than the treatment group. At one-year follow-up, both groups demonstrated statistically significant improvements compared with their status before the injections, but there was no differences between the groups. Weaknesses The authors utilized an ineffective or inappropriate placebo technique injecting sodium chloride solution through the transforaminal approach and large volumes were utilized. In this study the lumbar radiculitis lasted only for 3 to 28 weeks and failed to meet our inclusion criteria.	11/12

Table 12 (cont.). *Transforaminal epidural steroid injections either with placebo or active control.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths\ Weaknesses	Methodological Quality Assessment Score
Jeong et al, 2007 (47)	239 patients Patients with the presence of lumbosacral radiculopathy with clear nerve root compression documented with CT or MRI with the consensus of 3 radiologists.	Comparison of 2 approaches considered as active control trial. Ganglionic vs. preganglionic	Patients received either ganglionic or preganglionic TFESI under fluoroscopy. The patients received 0.5 mL of bupivacaine hydrochloride and 40 mg of 1 mL of triamcinolone. Number of injections=1	An outcome of 50% or more was considered effective.	Follow-up was conducted one month and 6 months after injection.	Results showed that the preganglionic group had a better result than the ganglionic approach but that at 6 months there was no difference between them.	Strengths: include that this was a randomized control trial. Other strengths include blinded patients and outcome assessor. Weaknesses: The weakness is that there was not an actual comparative group to evaluate the injected drugs. This is essentially a technical comparison. Adequacy of randomization and concealment of treatment allocation have not been well described. Similarly, care provider was not blinded.	9/12
Riew et al, 2000,2006 (59,132)	55 patients; lumbar radicular pain with radiographic confirmation of nerve-root compression. Each patient considered a surgical candidate by the patient and the surgeon.	Transforaminal injection with bupivacaine (n = 27).	Transforaminal epidural injections with bupivacaine and betamethasone (n = 28). Number of injections=1 to 4	Operative intervention	13-28 months post-injection	Significantly fewer patients in the intervention group (29%) pursued surgery, compared with the control group (67%).	Strengths: Significant follow-up (13-28 months). Patient and surgeon blinded to the intervention. Weaknesses: Secondary outcome measures only obtained for nonoperative group. Adequacy of randomization and conceal treatment allocation are lacking. In addition, dropout rates were not described.	8/12
Vad et al, 2002 (60)	48 patients; leg pain greater than back pain with symptoms > 6 wk, MRI with HNP with < 50% intervertebral foraminal narrowing.	Paraspinal saline trigger point injections (n = 23).	Transforaminal epidural injections with lidocaine and betamethasone (n = 25). Number of injections=1 to 3	Roland-Morris score, visual numeric pain score, finger to-floor distance, and a 0-4 patient satisfaction score.	Pre-injection, 3 and 6 weeks and 3, 6, and 12 months postinjection	At least 2 at one year post-injection, 84% of intervention group and 48% of control group had a successful outcome, which was statistically significant.	Strengths: Length of follow-up (1.4 y). Weaknesses: Trigger point injection was utilized as a control. The adequacy of randomization, concealment of allocation, patient blinding, care provider blinding, outcomes assessor blinding, and description of dropout rates was lacking.	5/12
Ng et al, 2005 (61)	86 patients; chronic unilateral radicular pain that failed conservative treatment.	A single transforaminal epidural injection with bupivacaine only (n = 43).	A single TFESI with bupivacaine and methylprednisolone (n = 43). Number of injections=1	Oswestry, VAS for back and radicular pain, change in walking distance, and patient's satisfaction level.	6 and 12 weeks postinjection.	Improvement in both groups for leg pain, Oswestry, and walking distance, but no statistically significant difference between the 2 groups.	Strengths: Patients were blinded to the intervention. Weaknesses: Duration of symptoms was greater in the treatment group compared with the controls. The control group is not a true placebo. Patients were limited to only one injection.	10/12

Table 12 (cont.). *Transforaminal epidural steroid injections either with placebo or active control.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths\ Weaknesses	Methodological Quality Assessment Score
Park et al, 2010 (125)	106 patients between 18 and 88 years, with a diagnosis of lumbar radicular pain based on an appropriate distribution of pain, and MRI showing nerve root compromise.	Active control trial comparing dexamethasone vs. triamcinolone.	Single transforaminal epidural steroid injection either with 7.5 mg dexamethasone or 40 mg triamcinolone mixed with 1 mL of 1% lidocaine. Number of injections=1	VAS, ODI, MPQ	Baseline and at 4 weeks after the procedure.	For the dexamethasone group, the reduction of pain score was 40%, whereas that of triamcinolone group was 71%.	Strengths: This is a randomized controlled trial comparing the effectiveness of non-particulate corticosteroids versus particulate steroids. Weaknesses: Very short-term follow-up with inadequate information to apply clinically. Randomization and concealment procedures were either not well described or inadequate. The blinding status of the outcome assessor is not known.	8/12
Burgher et al, 2011 (152)	26 patients with lumbar disc herniation were randomized to transforaminal epidural injections of 2% lidocaine and either 200 or 400 mcg of clonidine, or 40 mg of triamcinolone with lidocaine.	Active control-trial.	Transforaminal epidural injections administered at about 2 weeks apart. Number of injections=1 to 3	NRS, patient global impression change, MPI, Center for Epidemiologic Studies Depression Scale, RMDQ, ODI	Evaluation performed at 2 weeks and one month.	The addition of clonidine was superior to addition of triamcinolone.	Strengths: Double-blind randomized controlled trial. Weaknesses: Very short-term follow-up with a small number of patients with inability to reach conclusions with regards to effectiveness of either drug.	12/12
Devulder et al, 1999 (156)	60 patients; history of spinal surgery for disk herniation with EMG confirming chronic nerve pathology and imaging confirming nerve fibrosis.	Active-control trial with comparison of multiple drugs.	Transforaminal injection with bupivacaine, hyaluronidase (n = 20) vs. transforaminal epidural injection with bupivacaine, methylprednisolone (n = 20) vs. transforaminal epidural injection with bupivacaine, hyaluronidase, methylprednisolone (n = 20). Each group received 2 injections one week apart. Number of injections=2	Verbal rating score (0-4).	1, 3, 6 months post-injection.	There were no statistically significant differences between groups. Overall, pain relief was most prominent after one-month, but decreased at 3 and 6 months.	Strengths: Uniform patient selection—EMG and imaging to determine chronic nerve pathology. Weaknesses: Non-blinded study. Chronic nerve pathology population cannot be generalized. Patient baseline characteristics not given. Further, randomization, concealment of treatment allocation, blinding of the patients, blinding of provider, and blinding of outcome assessor were inadequate.	6/12
Tafazal et al, 2009 (162)	150 patients with radicular pain due to lumbar radiculitis either secondary to lumbar disc herniation or foraminal stenosis.	Active controlled trial either with bupivacaine alone or bupivacaine with 40 mg of methylprednisolone.	All patients received 2 mL of 0.25% bupivacaine alone or 2 mL of 0.25% bupivacaine and 40 mg of methylprednisolone. Number of injections=1	VAS, ODI, LBOS	6 weeks, 12 weeks, one year.	Both groups showed significant improvement; however, the addition of corticosteroids failed to provide any additional benefit compared to local anesthetic alone.	Strengths: Randomized, double-blind controlled trial with appropriate methodological quality in a fairly large number of patients. Weaknesses: No placebo control	10/12

Table 13. *Transforaminal epidural steroid injections compared with interlaminar, caudal epidural steroid injections ,or plasma disc decompression.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths	Methodological Quality Assessment Score
Park & Lee, 2011 (31)	A total of 55 patients with lumbar spinal stenosis to evaluate the prognostic usefulness of high sensitivity C-reactive protein.	There was no control.	Lumbar transforaminal epidural steroid injection under fluoroscopic guidance with 40 mg of triamcinolone and 1 mL of 1% lidocaine. Number of injections=1	VAS scores	4 weeks	There was correlation between pretreatment high sensitivity C-reactive protein and post treatment VAS.	Strengths: The authors attempted to evaluate prognostic usefulness of high-sensitivity C-reactive protein. Weaknesses: A study in a relatively small proportion of patients attempting to evaluate usefulness of sensitivity of C-reactive protein for transforaminal epidural steroid injections, with low methodological quality.	5/13
Gerszten et al, 2010 (52)	90 patients associated with a single-level lumbar contained disc herniation were enrolled in a multicenter study.	Active control trial	Plasma disc decompression or nucleoplasty in 46 patients and transforaminal epidural steroids injections in 44 patients. Number of injections: 1 to 2	VAS, ODI, SF-36	2 years	Patients in the plasma disc decompression or PDD group had significantly greater reduction in leg pain scores, ODI, and SF-36. During the 2-year follow-up, 56% of the patients in the PDD group and 28% of those in the transforaminal epidural group remained free from having a second procedure, following the study procedure.	Strengths: This is a prospective, randomized controlled trial performed at multiple centers. Weaknesses: The study compared 2 different types of treatments without correlation. A short-term transforaminal epidural injection which has been shown to provide approximately 12 weeks of relief was compared with a surgical procedure-plasma disc decompression.	7/12
Lee et al, 2009 (53)	95 patients with disc herniation 138 patients with spinal stenosis	Active-control trial	Interlaminar vs. transforaminal vs. caudal Number of injections=1	VAS, PSI	2 months	Higher ratio of successful results were found in interlaminar and transforaminal techniques than caudal technique.	Strengths: Comparison of 3 different techniques. Weaknesses: Very short-term follow-up	6/10
Lee et al, 2009 (72)	192 patients with a diagnosis of herniated intervertebral disc and spinal stenosis were selected based on clinical manifestations and MRI findings.	The study is a comparison of 2 techniques with outcomes of interlaminar and transforaminal epidural injections under fluoroscopy.	Interlaminar or transforaminal technique under fluoroscopy with 4 mL of lidocaine and 0.5 mL of triamcinolone acetonide Number of injections=1 to 3	NRS, PSI, and the Roland 5 point pain score.	4 months	In the spinal stenosis group, the transforaminal epidural steroid injection showed more significant benefits than interlaminar epidural steroid injection in pain reduction; whereas, in the herniated intervertebral disc group both were equal.	Strengths: The study was performed under fluoroscopy for both interlaminar, as well as transforaminal epidural injections in a large number of patients. Weaknesses: Short follow-up. The volume of injection was high with 4 mL of lidocaine and 0.5 mL of triamcinolone acetonide for transforaminal. Concealment of the concealed treatment allocation, patient blinding, care provided blinding, outcome assessor blinding were inadequate.	7/12

Table 13 (cont.). *Transforaminal epidural steroid injections compared with interlaminar, caudal epidural steroid injections, or plasma disc decompression.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths	Methodological Quality Assessment Score
Ackerman & Ahmad 2007 (73)	90 patients; L5-S1 disk herniation on imaging and severe S1 radicular pain with S1 radiculopathy on EMG.	Fluoroscopically guided caudal injection with triamcinolone and saline (n = 30) or fluoroscopically guided interlaminar epidural steroid injection with triamcinolone and saline (n = 30)	Transforaminal epidural steroid injection with triamcinolone and saline (n = 30) Average injections: Transforaminal: 1.5 Caudal: 2.5 Interlaminar: 2.2	Numeric pain score (0-10), rating of pain relief, Oswestry, Beck Depression score, contrast dispersion pattern.	2, 12, and 24 weeks, postinjection.	Transforaminal epidural steroid injection group had significantly more patients with complete and partial relief at 12 and 24 weeks. There were more reports of complete pain relief with ventral contrast spread.	Strengths: Uniform patient selection with all 3 modalities performed under fluoroscopy. Weaknesses: A small number of patients (30) in each group with relatively short duration of follow-up of 24 weeks with differential volumes and lack of blinding, etc.	7/12
Candido et al, 2008 (124)	57 patients with low back pain and unilateral radiculopathy with HNP, DDD, or spinal stenosis on imaging.	Fluoroscopically guided parasagittal interlaminar epidural steroid injection with methylprednisolone, lidocaine, and saline (n = 29).	Transforaminal epidural steroid injection with methylprednisolone, lidocaine, and saline (n = 28) Number of injections=1 to 3	Contrast flow pattern, fluoroscope time, VAS.	2 weeks postinjection and 1, 3, and 6 months postinjection.	VAS scores improved in both groups with no significant differences.	Strengths: Parasagittal ILESI approach was utilized. Weaknesses: Significant crossover. A small number of patients and relatively short period of follow-up.	7/12
Ng & Sell, 2004 (144)	Prospective evaluation of 125 consecutive patients with data available in 117 patients with 55 patients of lumbar disc herniation and 62 patients of spinal stenosis.	The authors compared the response to periradicular infiltration in patients with lumbar disc herniation or spinal stenosis.	Transforaminal epidural or as described, periradicular infiltration, with 2 mL of 0.25% bupivacaine and 40 mg of methylprednisolone. Number of injections=1 to 3	VAS, ODI, MZDS, MSPQ	3 months	The results showed there was a significantly better response to periradicular infiltration for radicular pain patients with lumbar disc herniation than the spinal stenosis.	Strengths: Moderate number of patients with 55 patients in the disc herniation group and 62 patients in the spinal stenosis group. Weaknesses: A short-term follow-up without a control group.	7/13
Manchikanti et al, 1999 (151)	225 patients receiving epidural injections by 3 routes which included patients with disc herniation, axial low back pain, and post lumbar surgery syndrome.	There was only a comparison of 3 techniques without control.	Blind interlaminar versus fluoroscopically guided caudal versus transforaminal. Number of injections=4.6 over a period of 2 years	Pain relief of > 50%	Over 12 months	Epidural administration of corticosteroids under fluoroscopy by caudal or transforaminal route was a valuable, safe, and cost-effective technique.	Strengths: Though this is a retrospective evaluation, patients were selected randomly from a large number of patients and also evaluated the cost-effectiveness. Weaknesses: This was a retrospective evaluation and the cost-effectiveness were considered as preliminary. Further, there was no homogeneity as lumbar interlaminar were performed without fluoroscopy.	6/10

Table 13 (cont.). *Transforaminal epidural steroid injections compared with interlaminar, caudal epidural steroid injections, or plasma disc decompression.*

Reference, Year	Number of Patients Selection Criteria	Control	Intervention	Outcome Measures	Time of Measurement	Results	Strengths	Methodological Quality Assessment Score
Rados et al, 2011 (155)	Randomized evaluation of 64 patients with chronic unilateral radicular pain caused by herniated disc.	Lumbar interlaminar versus lumbar transforaminal under fluoroscopy. Into each group, 32 patients were assigned.	Lumbar interlaminar epidural injection under fluoroscopy with local anesthetic and steroids or lumbar transforaminal epidural injection with local anesthetic and steroids. Number of injections=1 to 3	VAS, ODI	6 months is a rather short follow-up period.	There was no significant difference between both groups.	Strengths: The study compares both techniques under fluoroscopy. Weaknesses: A short-term follow-up in a rather small proportion of patients.	8/12
Mendoza-Lattes et al, 2009 (158)	Retrospective case-control study evaluating 93 patients with lumbar radiculopathy.	Comparison of transforaminal epidural with caudal epidural injection.	Caudal epidural steroid injections and transforaminal epidural injections, Marcaine 0.25% mixed with Depo-Medrol 40 mg per mL or Celestone 6 mg per mL with 1.5 to 2 mL solution. (up to 18 mg). Number of injections= 1 to 3	VAS, ODI, SF-36. The endpoint was surgical intervention.	Baseline, post treatment (< 6 months), long-term (> one-year)	The effectiveness of transforaminal epidural steroid injection was comparable to that of caudal epidural steroid injection with approximately 60% improvement in both groups for the treatment of primary lumbar radiculopathy.	Strengths: The authors compared transforaminal with caudal epidural utilizing fluoroscopy. Weaknesses: It is unclear if they have used local anesthetic for caudal epidural or not. Further, they also included patients with surgical interventions. Baseline characteristics of patients were not described.	6/10

PDD = plasma disc decompression; HNP = herniated nucleus pulposus; ILESI = interlaminar epidural steroid injection; EMG = electromyogram; VAS = visual analog scale; PSI = Patient Satisfaction Index; DDD = degenerative disk disease; ODI = Oswestry Disability Index; SF-36 = Short Form-36 Health Survey; MRI=magnetic resonance imaging; MSPQ= Modified Somatic Perception Questionnaire; MZDS = modified Zung depression scale.

has been judged as negative (3,4,62,169-171), and has been extensively criticized (2,11,62,172-175). Further, subgroup analysis also showed cost-effectiveness (134). Karppinen's study (58) failed to take into consideration that injecting sodium chloride solution into the transforaminal epidural space is not a true placebo. Significant arguments have been made for and against about what is an actual true placebo in interventional pain management. Finally, Ghahreman et al (120), for the first time, have designed and evaluated a true placebo for transforaminal epidural injections and have shown that sodium chloride intramuscular injection is not only a true placebo, but also that intramuscular steroids were ineffective. Various characteristics of these studies are illustrated in Tables 7 to 14.

Thus, questions regarding appropriate placebo must be dispelled. Further, the role of placebo substances injected into active spaces must be realized. The evidence by Ghahreman et al (120) illustrates the evidence that when injected into active structures, sodium chloride solution and local anesthetics are not placebos, rather they generate significant activity (62,69,101,102,104-114,175-194).

Among the randomized trials, there were 5 studies which included more than 100 participants (47,58,72,120,125). There were only 2 placebo-controlled trials and the remaining were active-control trials. However, there was only one properly conducted placebo-controlled trial (120), whereas the second one was inappropriately described as placebo-controlled; they also treated acute low back pain patients (58). Active-control trials ranged from comparing local anesthetic versus local anesthetic with steroid, technical variations (preganglionic versus postganglionic), types of steroids (long-acting vs. short-acting), and finally, transforaminals were also compared with interlaminar, caudal, and in one study, with plasma disc decompression (nucleoplasty).

The populations evaluated in all the included studies were consistent with the inclusion criteria with patients with disc herniation and leg pain. Even though studies combined spinal stenosis, discogenic pain, and post lumbar surgery syndrome, for this subject of evaluation – disc herniation - only the proportion of patients utilized for disc herniation were included (when described) as shown in Table 14.

Multiple studies illustrated significant improvement while comparing the baseline improvement with an appropriate follow-up period, some have shown significantly better improvement when steroid was added (47,53,59,73,120,124,125,144,151,152,155,158), whereas others have illustrated no significant improvement (61,162) with addition of steroid, even though similar evidence was also illustrated in an experimental study (195). However, only 4 studies compared bupivacaine plus corticosteroids (59,61,120,162). All of them showed positive results when local anesthetics were combined with steroids, with 2 studies showing positive results (59,120), whereas 2 studies showed equally effective results with bupivacaine alone compared to bupivacaine with steroids (61,162). None of the studies utilized lidocaine in comparing local anesthetic alone or with steroids.

Multiple studies also illustrated patients avoiding surgery when treated with transforaminal epidural injections (59,132,143,158,163).

Further results also illustrated transforaminal epidural injections may be superior to interlaminar epidural injections but inferior to plasma disc decompression, whereas some have provided equivalent results between interlaminar and caudal injections, but not inferior results.

2.5.1.1 Effectiveness

Of the 13 randomized trials meeting inclusion criteria for evaluating lumbar transforaminal epidural steroid injections, 5 trials (61,72,120,125,152) evaluated short-term results and 8 trials evaluated long-term results (47,52,58,59,73,124,155,162). There were 4 non-randomized studies (53,144,151,158) meeting inclusion criteria evaluating the effectiveness of transforaminal epidural injections of which 2 were short-term (53,144) and 2 were long-term (151,158).

Short- and long-term relief was evaluated in 13 randomized trials, of which 10 trials (47,59,61,72,73, 120,124,125,155,162) with 498 patients receiving steroids and 60 patients receiving local anesthetic only 2 (61,162) showed positive results. One randomized trial showed negative results (52) utilizing 44 patients in the steroid group. Negative results for local anesthetics were seen in 2 trials (59,120) with 54 patients. Further, 2 randomized trials (58,152) showed results which could not be determined: these included 15 patients receiving local anesthetic and steroids, 80 patients receiving sodium chloride solution and steroids, and 80 patients receiving normal saline.

Overall, long-term relief was illustrated in 6 of the 8 randomized trials evaluating long-term follow-up (47,59,73,124,155,162); whereas one trial (58) showed results which were undetermined and one trial (52)

Table 14. *Results of randomized and observational studies of effectiveness of transforaminal epidural injections in managing disc herniation or radiculitis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment(s)
					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, PLACEBO CONTROL																	
Ghahreman et al (120)	R, PC	12/12	Total=150 5 groups with 28, 37, 27, 28, 30	steroids with saline vs local anesthetic vs Intramuscular steroids vs Intramuscular saline Number of injections=1 to 3	Transforaminal saline=19% Transforaminal local anesthetic=7% Transforaminal epidural=54%	NA	NA	P	N	N	N	NA	NA	NA	NA	NA	This study was the first of its nature with a true placebo evaluation.
Karppinen et al (58,134)	R, PC	11/12	Total=160 Methylprednisolone-bupivacaine=80 Saline=80	Sodium chloride solution, or methylprednisolone (40 mg) and bupivacaine (5 mg) Number of injections=1	NA	SI in both groups	SI in both groups	U	U	U	U	U	U	U	U	U	An ineffective or inappropriate placebo technique.
RANDOMIZED, ACTIVE CONTROL																	
Jeong et al (47)	R, AC	9/12	Total=193 Ganglionic (G) = 104 Preganglionic (PG) = 89	0.5 mL of bupivacaine hydrochloride and 40 mg of 1 mL of triamcinolone Number of injections=1	PG=88.4% G=70.9%	PG=60.4% G=67.2%	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Multiple deficiencies noted in the quality assessment
Gerszten et al (52)	R, AC	7/12	Total = 90 PDD = 46 TF = 44	Plasma disc decompression or transforaminal Number of injections=2	NA	VAS and ODI 21% and PDD -49%,. vs 32%, and 15%	VAS and ODI - 18% PDD -44%, vs 25%, and 10%	U	NA	NA	N	NA	NA	N	NA	NA	The study evaluated 2 dissimilar modalities of treatments.
Riew et al (59,132)	R, AC	8/12	Total = 55 Bupivacaine = 27 Bupivacaine + steroid = 28	Bupivacaine 0.25% or bupivacaine with 6 mg of betamethasone Number of injections=1 to 4	NA	NA	33% vs 71% (avoided surgery)	P	U	NA	P	U	NA	P	N	NA	Surgery was avoided in 33% of bupivacaine group and 71% in the steroid group.

Table 14 (cont.). *Results of randomized and observational studies of effectiveness of transforaminal epidural injections in managing disc herniation or radiculitis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment(s)
					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	
Vad et al (60)	R, AC	5/12	Total = 48 Trigger point injections=23 Transforaminal epidural=25	trigger point injections or transforaminal epidural Number of injections=1 to 3	NA	NA	Roland-Morris Disability Scores 48% vs 84%	NA	NA	NA	NA	NA	NA	P	NA	NA	The study was not blinded.
Ng et al (61)	R, AC	11/12	Total =49 Bupivacaine=26 Bupivacaine + steroid=23	bupivacaine only, or bupivacaine with methylprednisolone. Number of injections=1	Bupivacaine =4 7.5% Bupivacaine + steroid = 41.5%	NA	NA	P	N	NA	NA	NA	NA	NA	NA	NA	Small study and short-term follow-up
Lee et al (72)	R, AC	7/12	Total=93 IL=34 TF=59	interlaminar vs transforaminal epidural injections. 4 mL (TF) Number of injections=1 to 3	Roland Pain Score Transforaminal = 3.34 to 1.59 Interlaminar = 3.25 to 1.57	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	short-term study
Ackerman & Ahmad (73)	R, AC	7/12	Total=90 Caudal = 30 Interlaminar = 30 Transforaminal = 30	Steroid and saline with local anesthetic Number of injections=1 to 3	Caudal = 57% Interlaminar =1 60% Transforaminal = 83%	Caudal = 57%) Interlaminar = 60% Transforaminal = 83%	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Relatively short-term follow-up with high volumes of injection.
Candido et al (124)	R, AC	7/12	Total=60 TF=30 PIL=30	lateral parasagittal interlaminar epidural or transforaminal epidural Number of injections=1 to 3	no significant difference between the groups 42.93 versus 46.6	Improvement in VAS scores from baseline but no differences between the groups	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Focus on the contrast medium spread and the related relief.
Park et al (125)	R, AC	7/12	Total =1 06 Dexamethasone =5 3 Triamcinolone acetate = 53	Dexamethasone or triamcinolone acetate with lidocaine. Number of injections=1	Dexamethasone = 40% triamcinolone = 71%.	NA	NA	P**	NA	NA	NA	NA	NA	NA	NA	NA	Triamcinolone was more effective than dexamethasone.

Table 14 (cont.). *Results of randomized and observational studies of effectiveness of transforaminal epidural injections in managing disc herniation or radiculitis.*

Study	Study Character-istics	Method-ological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment(s)
					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	
Burgher et al (152)	R, AC	12/12	Total = 26 Clonidine = 11 Triamcinolone = 15	Lidocaine with clonidine, or 4 triamcinolone Number of injections=1 to 3	SI in both groups	NA	NA	U	NA	NA	NA	NA	NA	NA	NA	NA	Small study
Rados et al (155)	R, AC	8/12	Total=64 IL=32 TF=32	Interlaminar vs transforaminal Number of injections = 1 to 3	TF=53% IL=75%	TF=53% IL=75%	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Short-term follow-up period
Tafazal et al (162)	R, AC	10/12	Total=76 Bupivacaine = 34 Bupivacaine + steroid = 42	Bupivacaine with methylprednisolone Number of injections = 1 to 3	VAS and ODI change Bupivacaine = 24.3 and 13.8 Bupivacaine + steroid = 27.4 and 13.6	P	NA	P	P	NA	P	P	NA	P	P	NA	No differences
NON-RANDOMIZED																	
Ng & Sell (144)	NR, PR	7/13	Total=55 Periradicular infiltration	Bupivacaine with methylprednisolone. Number of injections=1 to 3	NSCH	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Small number of patients with short follow-up.
Lutz et al (128)	NR, PR	6/13	Total=69	Betamethasone acetate with Xylocaine Number of injections=1 to 4	NA	NA	78.3%	NA	NA	NA	NA	NA	NA	P	NA	NA	Prospective case series showing positive results
Lee et al (53)	NR, RE	6/10	Total = 95 Four groups with 50, 31, 14 or 12	Lidocaine with triamcinolone Number of injections=1	Transforaminal = 65.8% Interlaminar = 51.6% Caudal = 21.4%	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Transforaminal was superior to caudal; however, equal to interlaminar..
Rosenberg et al (131)	NR, RE	6/13	Total = 34	Methylprednisolone mixed with lidocaine with epinephrine and bupivacaine. Number of injections = 1 to 4;	68%	56%	59%	P	NA	NA	P	NA	NA	P	NA	NA	Small study

Table 14 (cont.). *Results of randomized and observational studies of effectiveness of transforaminal epidural injections in managing disc herniation or radiculitis.*

Study	Study Character-istics	Method-ological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment(s)
					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	
Berger et al (146)	NR, RE	6/13	Total = 80	Lidocaine with hydrocortisone Number of injections = 1 to 3	45 of 68 (66%)	45 of 68 (66%)	35 of 68 (51%)	P	NA	NA	P	NA	NA	P	NA	NA	A retrospective evaluation with positive results.
Mendoza-Lattes et al (158)	NR, RE, CC	6/10	Total = 93 Caudal = 39 Transforaminal =54	Marcaine with Depo-Medrol or Celestone. Number of injections=1 to 3	Surgery avoided in caudal group -59%, in transforaminal	Surgery avoided in caudal group -59%, in transforaminal-55.6%	Surgery avoided in caudal group -59%, in trans-foraminal epidural-55.6%	P	NA	NA	P	NA	NA	P	NA	NA	Patients improved, equally with avoidance of surgery.
Wang et al (163)	NR, RE	6/13	Total = 69	Transforaminal epidural steroid injections Number of injections 1-6	77%	77%	77%	P	NA	NA	P	NA	NA	P	NA	NA	Long-term positive study

R = randomized; PC = placebo control; AC = active-control; NR = non-randomized; PR = prospective; RE = retrospective; CC = case-control; IL = interlaminar TF = transforaminal; NSCH = no significant change; P = positive; N = negative; NA = not applicable; U = unclear; G = ganglionic; PG = preganglionic; PDD = plasma disc decompression; PIL = parasagittal interlaminar; ST = steroid; LA = local anesthetic; SAL = saline; VAS = visual analog scale; ODI = Oswestry Disability Index; CT = computed tomography; ** = triamcinolone compared dexamethasone

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

Study	Study Charact-eristics	Methodo-logical Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment (s)
					3 mos.	6 mos.	12 mos	Short-term ≤ 6 mos.			Long-Term > 6 mos			Long-Term ≥ 1 year			
								ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
RANDOMIZED																	
Jeong et al (47)	R, AC	9/12	Total=46 Ganglionic=23 Preganglionic = 23	Bupivacaine withtriamcinolone Number of injections=1	89.1%	56.5%	NA	P	NA	NA	P	NA	NA	NA	NA	NA	Multiple deficiencies noted in the quality assessment
Ng et al (61)	R, AC	11/12	Total=32 Bupivacaine = 15 Bupivacaine + steroid=17	Bupivacaine only, or bupivacaine with methylprednisolone. Number of injections = 1-2	Pain and ODI Bupivacaine = 47.5% and 41.5%	NA	NA	P	P	NA	NA	NA	NA	NA	NA	NA	A small number of patients with short follow-up period.
Lee et al (72)	R, AC	7/12	Total=99 IL=42 Bilateral TF=57	Lidocaine with triamcinolone Number of injections=1 to 3	Transforaminal = 3.34 to 1.59 Interlaminar = 3.25 to 1.57	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Bilateral transforaminal epidural steroid injections were superior.
Tafazal et al (162)	R, AC	10/12	Total = 48 Bupivacaine= 25 Bupivacaine + steroid = 23	Bupivacaine or bupivacaine with methylprednisolone Number of injections=1 to 3	VAS and ODI change Bupivacaine = 20.4 and 6.5 Bupivacaine + steroid = 19.4 and= 1.5	NA	NA	N	N	NA	N	N	NA	N	N	NA	Disc herniation showed superior results.
NON-RANDOMIZED																	
Park & Lee (31)	NR, PR	5/13	Total=55	Triamcinolone and lidocaine Number of injections=1	Significant improvement	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	No prognostic usefulness of high sensitivity C-reactive protein.
Lee et al (53)	NR, RE	6/10	Total = 138 Interlaminar = 33 Caudal = 40 Transforaminal = 49	Lidocaine with triamcinolone Number of injections=1	Transforaminal = 53% Interlaminar = 57.6% Caudal=30%	NA	NA	P	NA	NA	NA	NA	NA	NA	NA	NA	Transforaminal was superior to caudal; however, equal to interlaminar..

Table 15 (cont.). *Results of randomized and observational studies of effectiveness of transforaminal epidural injections in managing spinal stenosis.*

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Results												Comment (s)
					Pain Relief and Function			Short-term ≤ 6 mos.			Long-Term > 6 mos			Long-Term ≥ 1 year			
					3 mos.	6 mos.	12 mos	ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
Cooper et al (127)	NR, RE, CC	6/13	Total=61	Triamcinolone with lidocaine	44.2%	NA	37.2%	P	NA	NA	NA	NA	NA	N	NA	NA	Negative study
Rosenberg et al (131)	NR, RE	6/13	Total=26	methylprednisolone with 1 mL of 1.5% lidocaine with epinephrine Number of injections=1 to 4	54%	19%	35%	P	NA	NA	N	NA	NA	N	NA	NA	Small study with only 26 patients with spinal stenosis.
Ng & Sell (144)	NR, P, RE	7/13	Total=62	Bupivacaine and methylprednisolone. Number of injections= Unclear	Mean change of VAS of 1.2, ODI change of at least 10% in 37%.	NA	NA	N	NA	NA	NA	NA	NA	NA	NA	NA	Negative study

R = randomized; AC = active-control; NR = non-randomized; RE = retrospective; PR = prospective; CC = case-control; P = positive; N = negative; NA = not applicable; VAS = visual analog scale; ODI = Oswestry Disability Index; IL = interlaminar; TF = transforaminal

showed negative results. A total of 538 patients were included in the positive studies and a total of 90 patients were included in the study with negative results.

Among the non-randomized studies, there were only 2 studies evaluating long-term follow-up (151,158). Of these, one study showed positive long-term results with 54 patients (158) receiving transforaminal injections.

2.5.2 Axial Pain

There were 3 non-randomized studies (131,146,151) evaluating the role of transforaminal epidural injections in patients without disc herniation, radiculitis, facet joint or sacroiliac joint pain.

2.5.2.1 Effectiveness

Rosenberg et al (131), Berger et al (146), and Manchikanti et al (151) studied the role of transforaminal epidural injections in managing discogenic pain without radiculitis or disc herniation. However, these studies included a small number of patients. Thus, there were no data for assessment of the evidence.

2.5.3 Spinal Stenosis

Table 15 illustrates the characteristics of the included studies. There were a total of 4 randomized trials (47,61,72,162) and 2 non-randomized studies (53,144) which met inclusion criteria based on quality assessment evaluating the role of transforaminal epidural injections in managing spinal stenosis. Of these, one trial (72) included 99 patients, whereas one study (53) included 138 patients suffering with spinal stenosis.

2.5.3.1 Effectiveness

Of the 4 randomized active-controlled trials (47,61,72,162), only 3 trials (47,61,72), which included 46 patients, 17 patients, and 57 patients receiving local anesthetic with steroids, showed positive results both short-term and long-term (47,61,72). One randomized trial (162), with 23 patients receiving bupivacaine with steroids, had negative results for steroids. Among the non-randomized studies, one study (53), which included 49 patients, showed positive results for short-term improvement and a second study (144) with 62 patients showed negative results for short-term improvement.

2.5.4 Post Surgery Syndrome

There was only one randomized trial with adequate data for describing and evaluating the role of transforaminal epidural steroid injections in post surgery syndrome (156).

2.5.4.1 Effectiveness

Devulder et al's study (156) was an active-control trial of 60 patients with a history of spinal surgery for disk herniation who had an electromyogram (EMG) to confirm chronic nerve pathology and imaging to confirm nerve fibrosis. Patients were treated with bupivacaine and hyaluronidase; bupivacaine and methylprednisolone; or bupivacaine, hyaluronidase, and methylprednisolone. There were no statistically significant differences among the groups. Overall, pain relief was most prominent after one month, but decreased at 3 and 6 months.

2.6 Level of Evidence

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

2.6.1 Lumbar Disc Herniation

For lumbar disc herniation with radiculitis, based on 10 positive randomized studies (47,59,61,72,73,120, 124,125,155,162), one negative study (52), and 2 studies with undetermined conclusions (58,152), the evidence is considered good for short-term and long-term relief with local anesthetics with steroids.

Of the 4 randomized trials comparing local anesthetic with steroids (59,61,120,162), 2 of them showed positive results (61,162), whereas 2 of them showed negative results (59,120), yielding fair evidence for short- and long-term relief with local anesthetic only.

There was fair evidence that transforaminal epidural injections will prevent surgery in a reasonable proportion of patients (59,132,143,158,163).

2.6.2 Axial Pain

There was no significant evidence for transforaminal epidural steroid injections in patients without radiculitis secondary to disc herniation or spinal stenosis.

2.6.3 Spinal Stenosis

For spinal stenosis, available evidence is fair based on 2 long-term randomized trials (47,162), 2 short-term randomized trials (61,72), 3 short-term non-randomized studies (31,53,144), with 3 studies showing positive results in short-term (31,53,72) and poor for long-term based on one positive active-control (47) and one negative control trial (162) for transforaminal epidural with local anesthetic and steroids.

2.6.4 Post Surgery Syndrome

The evidence for post lumbar surgery syndrome was poor based on one moderate quality randomized controlled trial (156), which was an active-control trial with indeterminate conclusions.

2.6.5 Summary of Evidence

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

3.0 Complications

The most common and worrisome complications of transforaminal epidural steroid injections in the lumbar spine, though rare, are related to neural trauma, vascular trauma, intravascular injection, and infection (14,24,25,29,196-215). None of the studies included in an effectiveness analysis showed any major complications.

In an academic physiatry practice over a 7-year period, McGrath et al (214) retrospectively evaluated the incidence and characteristics of complications from epidural steroid injections. They (214) published the results of 4,265 injections on 1,857 patients over 7 years with 161 cervical interlaminar injections, 123 lumbar interlaminar injections, 17 caudal injections, and 3,964 lumbar transforaminal injections; there were no thoracic epidural injections. They identified a lack of major complications and reported 103 minor complications, for an overall complication per injection rate of 2.4%.

Karaman et al (22) assessed the complications of transforaminal lumbar epidural steroid injections. They reported a total of 1,305 episodes of lumbar transforaminal epidural steroid injections in 562 patients. The overall incidence of vascular penetration encountered was 7.4%. However, major complications were not seen. The overall total rate of all minor complications was 11.5%. In this study they reported 8.7% vasovagal reactions.

Botwin et al (24) reported complications in 207 patients receiving 322 transforaminal lumbar epidural steroid injections. Complications included transient headaches in 3.1%, increased back pain in 2.4%, increased leg pain in 0.6%, facial flushing in 1.2%, vasovagal reaction in 0.3%, increased blood sugar in 0.3%, and hypertension in 0.3%. The incidence of minor complications was 9.6% per injection with no major complications.

Furman et al (209) reported that among the 761

transforaminal epidural steroid injections included in the study, the overall rate of intravascular injection was 11.2%, with a higher rate of intravascular injections (21.3%) at the S1 transforaminal compared with those at the lumbar levels (8.1%).

Manchikanti et al (14) reported intravenous placement of the needle in 22% of the procedures. Other complications included pain during the injection with back pain in 43% of the patients and leg pain in 22% of the patients. Postoperative complications were reported in 34% of the patients with soreness at the injection site in 18%, increased pain in 5%, muscle spasms in 4%, swelling in 4%, headache in 3%, minor bleeding in 2%, dizziness in 1%, nausea and vomiting in 1%, fever in 1%, numbness in 1%, and voiding difficulty in 1%.

Huston et al (196) reported no major complications noted and 91% of the patients had no side effects during the injection. The most common side effect noted was increased pain at the injection site after the injection, which was seen in 17.1% of the lumbar patients.

Goodman et al (213) in their description of complications and pitfalls of lumbar interlaminar and transforaminal epidural injections concluded that complications from lumbar epidural injections are extremely rare. Most if not all complications can be avoided by careful technique with accurate needle placement, sterile precautions, and a thorough understanding of the relevant anatomy and contrast patterns on fluoroscopic imaging.

However, transforaminal injections have been reported with complications including spinal cord injury and infarction and paraplegia (25,29).

Side effects related to the administration of steroids are generally attributed either to the chemistry or to the pharmacology of steroids (197). The major theoretical complications of corticosteroid administration include the suppression of pituitary adrenal axis, hyperadrenocorticism, Cushing syndrome, osteoporosis, avascular necrosis of the bone, steroid myopathy, epidural lipomatosis, weight gain, fluid retention, and hyperglycemia (198,199). Radiation exposure is also a potential problem with damage to eyes, skin, and gonads (200,201).

4.0 Discussion

This systematic review evaluating the effectiveness of lumbar transforaminal epidural injections in managing chronic low back and lower extremity pain caused by disc herniation with radiculitis showed good evidence for them. However, the evidence is fair for spinal stenosis. There was no evidence available for axial pain in the literature. For lumbar radiculitis in post surgery syndrome, evidence is limited.

In this evaluation, a total of 13 randomized trials and 5 non-randomized studies were included. Only the studies meeting at least moderate quality criteria were included in analysis. A quality assessment for all the manuscripts was performed. This rigorous review yielded similar results to Buenaventura et al (11) published in 2009, a critical review of APS guidelines (62,187), and a reassessment of the American College of Occupational and Environmental Medicine (ACOEM) guidelines (216). However, these results do not correlate with results by Chou and Huffman (4) and Staal et al (92). Further, results provided by other reviewers are also in line with the evidence from this review (65,66,68,71).

Roberts et al (65), in a systematic review of the efficacy of lumbosacral transforaminal epidural steroid injections, extensively discussed not only the effectiveness, but also their role in avoiding surgical interventions. They concluded that there was fair evidence supporting transforaminal epidural steroid injections as superior to placebo for treating radicular symptoms, and there was good evidence that transforaminal epidural steroid injection should be used as a surgery-sparing intervention. They also concluded that transforaminal epidural injections were superior to interlaminar epidural injections and caudal epidural injections for radicular pain. However, they raised multiple issues related to challenges facing the determination of global recommendations based on the available evidence. They noted that the body of evidence contained very heterogenous studies with significant differences in the study populations, controls used, duration of follow-up, outcome measures, the type of intervention, number of injections, the technical approaches, types of medications, and volume of injection. In the present systematic review, we also echo the findings of Roberts et al (65) with the same issues. However, the present evaluation showed only limited evidence for superiority of transforaminal epidural injections over caudal or interlaminar epidural injections performed under fluoroscopy. In contrast, the evidence in this manuscript correlates with their conclusions that transforaminal epidural steroid injections are effective in avoiding surgical interventions.

Rho and Tang (71) concluded that there was strong evidence to support the use of lumbar transforaminal epidural injections in patients with acute to subacute unilateral radicular pain caused by herniated nucleus

pulposus or spinal stenosis. They also concluded that the relief was short-lived and that transforaminal epidural injections are an effective strategy for sparing a surgical procedure that should be a part of conservative care in the management of low back pain with radiculopathy. Our results also agree with the findings of Rho and Tang regarding to multiple variations in injection therapy and their effectiveness, which is rather short-lived and has a surgery-sparing effect. This also illustrates the flaws of multiple studies where the injections were performed on only one to 3 occasions, expecting a long-term relief of one to 2 years with gradually fading response; it may be expected that a patient may require 2 injections in the diagnostic phase, and 4 injections per year in the therapeutic phase (2,217-219).

Benny and Azari (68), in their comprehensive literature review of the efficacy of lumbosacral transforaminal epidural steroid injections evaluating 10 randomized trials, 4 retrospective studies, and 8 prospective studies, showed that 9 prospective trials showed positive short-term and long-term outcomes. They also, as others have, noted multiple variables; however, multiple studies they included in their evidence synthesis failed to be meet the criteria established in this systematic review. Overall, our results are in agreement with those of Benny and Azari (68).

In contrast to the above, Quraishi (67) provided somewhat different conclusions based on the meta-analysis he performed on epidural steroid injections. He concluded that transforaminal epidural steroid injections, when appropriately performed, should result in an improvement in pain, but not disability. He also stated that the 3 RCTs that followed patients to 3 months, and the single study of 12 months found no benefit by adding steroids. While the limits of his systematic review and meta-analysis were caused by the paucity of the available literature, there may also be multiple other deficiencies in this systematic review and meta-analysis. In contrast to Quraishi's conclusions, the results of the present systematic review show that transforaminal epidural injections not only improve pain and function, but also prevent surgery in a significant proportion of patients.

In contrast, Chou and Huffman (4), Staal et al (3), and ACOEM guidelines (170) provided different conclusions. Chou and Huffman in their evaluation stated that most placebo-controlled trials evaluated either the interlaminar or caudal approach. They concluded that 3 higher quality, placebo-controlled trials evaluating the transforaminal approach reported mixed results (58,59,61). However, of the 3, only one study utilized a placebo-controlled design and this design was inappropriate because of the inclusion of subacute pain patients (2,11,62,172-175). Consequently, these conclusions do not apply to chronic pain management with transforaminal epidural steroid injections. Further, Riew et al (59) showed the effectiveness of bupivacaine, which is not a placebo as interpreted by Chou and Huffman, showing significant improvement and avoidance of surgery in a significant proportion of patients in both groups, even though bupivacaine and steroids were superior to bupivacaine alone. Ng et al (61) was also an active-controlled trial with bupivacaine or bupivacaine plus steroids in a small proportion of patients. There were 26 patients in the bupivacaine group and 23 patients in the bupivacaine and steroid group. Similar results were shown for both groups with or without steroids. Thus, they concluded that for low back pain with sciatica, evidence for the efficacy of epidural steroid injection by the transforaminal approach was mixed, with 2 of 3 higher quality trials showing no benefit compared to control injections. As described, this is an inaccurate conclusion based on multiple flaws in the assessment.

Staal et al (3) evaluated all epidural injections in combination, including together caudal, lumbar interlaminar, and lumbar transforaminal as one category. They also failed to separate the response to herniation, stenosis, post laminectomy syndrome, or discogenic pain, consequently reaching inappropriate conclusions. Thus, the present systematic review contradicts this evidence.

ACOEM guidelines (170) provided a negative recommendation based on a review of Karppinen et al (58) and Ng et al (61). However, a critical assessment by Manchikanti et al (216) provided moderate to strong evidence.

The American Society of Anesthesiologists (ASA) and the American Society of Regional Anesthesia and Pain Medicine (ASRA) guidelines (220) utilized combined physician consensus with a systematic review; they also recommended epidural steroid injections.

The present systematic review shows that transforaminal epidural steroid injections, when appropriately performed, should result in significant improvement. These procedures can reduce the patient's pain, disability, and depression. Considering the low risk and less expensive nature of the procedure, compared to surgical interventions, transforaminal epidural injections with or without steroids seem to be cost effective.

With caudal and interlaminar epidurals, a common problem encountered is inaccurate needle placement, leading to inaccurate placement of the injectate. However, that is not an issue with transforaminal epidurals as it is required that transforaminal epidurals always be performed under fluoroscopy and that contrast injection medium first be injected (16,221-224). Even then, there has been controversy regarding the spread of the contrast medium associated with transforaminal epidural injections (14,39,73,225-227), showing a lack of ventral filling in some cases.

Placebo-controlled neural blockade is not realistic even though it has been misinterpreted (228). Some have mistakenly reported that any local anesthetic injection which yields similar results as steroids is considered a placebo. The experimental and clinical findings from investigation of the electrophysiological effects of 0.9% sodium chloride and dextrose 5% in water solution have illustrated a potential inaccuracy created by 0.9% sodium chloride solution versus 5% dextrose (181,182). Further, the evidence also has shown differing effects of sodium chloride solution when injected into either the disc, the facet joint or paraspinal muscles, with interaction between the porcine lumbar intervertebral disc, zygapophysial joints, and paraspinal muscles (183,184). They showed that the introduction of lidocaine or physiologic saline into the zygapophysial joint reduced the stimulation pathway from the intervertebral disc to the paraspinal musculature (183,184). Consequently, they hypothesized that the paraspinal muscle activation caused by nerve stimulation in the annulus fibrosus of a lumbar intervertebral disc could be altered by saline injection into the zygapophysial joint. Further, epidural saline has been shown to be active and therapeutic (185,186,194). Finally, for the placebo effect to be evident, it has to be non-existent with prior treatments, and present repeatedly.

Thus, both of the placebo-control studies utilized in the present evaluation (58,120) deserve attention. Only one of the 2 studies was appropriately performed. The study by Ghahreman et al (120) utilized appropriate placebo - sodium chloride solution, by injecting into inactive tissue. In contrast, Karppinen et al (58) utilized transforaminally injected sodium chloride solution in acute pain patients, which does not meet the criteria for our chronic pain settings which tends to avoid placebo responses as many of them undergo various types of investigations. Even then, they showed positive results in patients with disc herniation without extrusion and the procedures were cost-effective (134).

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 (2,197). 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 (197,229-233). 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 (195,233-240). The prolonged effect of local anesthetics in epidural injections and facet joint nerve blocks has been demonstrated in multiple studies (100-114,241-243). Sato et al (240) 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 (195) showed in rats that nerve root infiltration prevented mechanical allodynia; however, no additional benefit from using corticosteroid was identified.

Further discussions regarding the superiority of transforaminal epidurals over either caudal epidural injections or interlaminar epidural injections is not proven by this systematic review. However, this systematic review shows the ability of transforaminal epidural injections to prevent the need for surgical interventions. Further, based on this systematic review, the superiority of a depo steroid compared to either clonidine or dexamethasone has not been established. Thus, debate continues on multiple issues.

With reference to the complications, multiple devastating complications have been reported in patients undergoing transforaminal epidural injections in the lumbar spine, though less commonly than the thoracic and cervical spine. There also has been significant discussion on entry level to the foramen with the safe and unsafe triangle. Multiple techniques have been described to avoid radicular artery injection or trauma. However, none of these have been based on controls, experimental, or evidence-based. The arterial innervation does illustrate that the presence of artery in the inferior part of the foramen compared to the superior part other than this conjuncture (36). Based on case re-

ports, it appears that radicular artery injection is associated with significantly increased risk on the left side (L3 and above), in post surgery patients, multiple attempts during the procedure, known intravascular penetration, technical consideration with a sharp needle or performing the procedure in the upper part of the foramen, and finally, injection of particulate steroids.

The results of this systematic review may be applied in interventional pain management practices utilizing appropriate evaluations (62,69,70,110-114,187,216). 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 (76,77,83,84,114,244-247). 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 compare the therapies (248). 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 able to find only 25 appropriately performed studies which met inclusion criteria and were clinically relevant. 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. Transforaminal epidural injections show a significant reduction in pain scores for patients with lumbar radiculitis when compared to doing nothing, and conservative management without injection therapy (9).

The future implications for research should include a clear case definition with consistent inclusion and exclusion criteria, technical consideration, frequency, type and volume of injectate, outcome measures, appropriate design, and reporting of randomized trials (76,77,87,249,250). Ghahreman and Bogduk (30) evaluated predictors of a favorable response to transforaminal injection of steroids. They evaluated 71 patients with lumbar radicular leg pain caused by disc herniation treated with transforaminal epidural steroid injections as part of a randomized clinical trial. They analyzed clinical features of the presence of neurological symptoms, neurological signs, and the duration of sciatica, along with radiologic features of segmental level of pathology, the location and morphological features of disc herniation, the cross-sectional area of the disc herniation and its ratio to the cross-sectional area of the spinal canal, and the grade of nerve root compression. The results showed that none of the clinical features were associated with a successful outcome from the treatment. The only radiological feature associated with a successful outcome was the grade of nerve root compression. Thus, they showed that transforaminal epidural steroid injection is more often successful in patients without significant compression of the nerve root and, therefore, in whom an inflammatory basis for radicular pain is most likely. In such patients, a success rate of 75% renders transforaminal epidurals as an attractive alternative to surgery. Only 26% of patients with high-grade nerve root compression responded similarly. Thus, in patients with significant nerve root compression, the relief may be similar to placebo effect and surgery may be a more appropriate consideration. It follows that many of the studies which included patients with significant nerve root compression may have produced negative results similar to those of placebo.

5.0 Conclusion

In summary, the evidence is good for the effectiveness of therapeutic lumbar transforaminal epidurals for radiculitis secondary to disc herniation with local anesthetics and steroids and fair with local anesthetic only; whereas it is fair for radiculitis secondary to spinal stenosis with local anesthetic and steroids, and limited for axial pain and post surgery syndrome with local anesthetic with or without steroids.

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