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Systematic Review

Effectiveness of Cervical Epidural Injections in the Management of Chronic Neck and Upper Extremity Pain

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Background: Chronic persistent neck pain with or without upper extremity pain is common in the general adult population with prevalence of 48% for women and 38% for men, with persistent complaints in 22% of women and 16% of men. Multiple modalities of treatments are exploding in managing chronic neck pain along with increasing prevalence. However, there is a paucity of evidence for all modalities of treatments in managing chronic neck pain.

Cervical epidural injections for managing chronic neck pain are one of the commonly performed interventions in the United States. However, the literature supporting cervical epidural steroids in managing chronic pain problems has been scant.

Study Design: A systematic review of cervical interlaminar epidural injections for cervical disc herniation, cervical axial discogenic pain, cervical central stenosis, and cervical postsurgery syndrome.

Objective: To evaluate the effect of cervical interlaminar epidural injections in managing various types of chronic neck and upper extremity pain emanating as a result of cervical spine pathology.

Methods: The available literature on cervical interlaminar epidural injections in managing chronic neck and upper extremity pain were reviewed. The quality assessment and clinical relevance criteria utilized were the Cochrane Musculoskeletal Review Group criteria as utilized for interventional techniques for randomized trials and the criteria developed by the Newcastle-Ottawa Scale criteria for observational studies.

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

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

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

Results: For this systematic review, 34 studies were identified. Of these, 24 studies were excluded and a total of 9 randomized trials, with 2 duplicate studies, met inclusion criteria for methodological quality assessment.

For cervical disc herniation, the evidence is good for cervical epidural with local anesthetic and steroids; whereas, it is fair with local anesthetic only.

For axial or discogenic pain, the evidence is fair for local anesthetic, with or without steroids.

For spinal stenosis, the evidence is fair for local anesthetic, with or without steroids.

For postsurgery syndrome, the evidence is fair for local anesthetic, with or without steroids.

Limitations: The limitations of this systematic review continue to be the paucity of literature.

Conclusion: The evidence is good for radiculitis secondary to disc herniation with local anesthetics and steroids, fair with local anesthetic only; whereas, it is fair for local anesthetics with or without steroids, for axial or discogenic pain, pain of central spinal stenosis, and pain of post surgery syndrome.

Key words: Cervical disc herniation, cervical axial discogenic pain, cervical central spinal stenosis, cervical post surgery syndrome, cervical radiculitis, cervical interlaminar epidural injections, local anesthetic, steroids

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Chronic persistent neck pain has been reported to be present in almost 50% of the individuals who report neck pain at some point (1-3). Further, neck pain is common in the general adult population with a prevalence of 48% in women and 38% in men, with persistent complaints of 22% in women and 16% in men. Studies of the prevalence of chronic neck pain (1-11) and its impact on general health (6,11,12) showed 14% of patients reporting Grade II to IV neck pain with high pain intensity with disability. Similar to low back pain, neck pain is also associated with significant economic, societal, and health impact, though not to the same extent as low back pain. In fact, neck pain has been well recognized as a source of disability in the working population (13-17). In addition, motor vehicle injuries result in 24% to 50% of those involved with persistent symptoms at 12 months (18,19).

Multiple structures causing neck and upper extremity pain and headache include cervical intervertebral disc, cervical facet joints, atlanto-axial and atlanto-occipital joints, ligaments, fascia, muscles, and nerve root dura which are capable of transmitting pain. However, very little is known about the causes of neck pain. The epidemiologic studies do not reveal either the source or the cause of pain. Bogduk (20) described that neck pain and cervical radicular pain are distinct entities. Neck pain may be due to zygapophyseal or facet joints and intervertebral discs of the neck. Cervical radicular pain is pain perceived in the upper extremity, shooting or electric in quality, caused by irritation and/or injury of a cervical spinal nerve (20,21). Cervical radiculopathy is a neurological condition characterized by objective signs of loss of neurologic function: some combination of sensory loss, motor loss, or impaired reflexes, in a segmental distribution, however, without description of pain. Consequently, cervical radicular pain cannot be similarly attributed to the same cause as those of radiculopathy. Compression of axons does not elicit pain (20). If compression is to be invoked as a mechanism for pain it must explicitly relate to the compression of a dorsal root ganglion (22). In fact, laboratory experiments on lumbar nerve roots have shown that mechanical compression of nerve roots does not elicit activity in nociceptive afferent fibers (23). However, compression of a dorsal root ganglion does evoke sustained activity in afferent fibers; but, that activity occurs in A-beta fibers as well as C-fibers (23). Thus, in contrast to compression, there is growing evidence that cervical radicular pain may be caused by inflammation of the cervical nerve roots (20). This mechanism might be applicable to radicular pain caused by disc protrusions because inflammatory exudates have now been isolated from cervical disc material (24,25). The study from the Mayo Clinic shows an annual incidence of cervical radicular pain of 83 per 100,000 (26). According to this study, the most frequently involved level was C7 in 45% to 60% of the cases. Lotz and Ulrich (27) described that symptoms derived from a degenerated disc may be classified into 2 types: type 1, radicular pain secondary to stenosis and nerve root, and, type 2, discogenic pain due to internal disc disruption. Bogduk and Aprill (28) investigated the prevalence of zygapophysial and discogenic pain and the results showed discogenic pain without zygapophysial joint pain in 20% of the sample, whereas both a symptomatic disc and a symptomatic zygapophysial joint were identified in the same segment in 41% of the patients. Thus, based on controlled diagnostic blocks, cervical facet joints have been implicated as being responsible for pain in the neck, head, and upper extremities in 36% to 67% of patients (29-36), whereas reports of cervical discogenic pain (28,29) show a prevalence of 16% to 20%. Further, Yin and Bogduk (29) reported that of the 143 patients with chronic neck pain, only 5 patients were diagnosed with cervical radicular pain on the basis of history and clinical examination, while the remaining patients had idiopathic neck pain. It has been shown that, by far, the most common causes of cervical radicular pain are disc protrusion and cervical spondylosis (21,26,37-43).

Numerous modalities of treatments have been described in managing chronic persistent neck pain with or without upper extremity pain (21,44-71), with exploding costs creating a health care financial crisis. Epidural injections for managing chronic neck pain are one of the commonly performed interventions in the United States (64,67,69-74). Cervical epidural injections have been used to treat radicular pain from herniated discs, spinal stenosis, chemical discs, chronic pain secondary to postcervical surgery syndrome, and chronic neck pain of discogenic origin. Epidural injections in the cervical spine are performed either by interlaminar or transforaminal approaches. Cervical epidural steroid injections, specifically utilizing the transforaminal approach, have been associated with significant complications (75-85). These complications are much more severe and significant with the transforaminal approach (75,76). However, significant complications also have been reported with interlaminar epidurals with spinal cord damage and quadriparesis (77,78). Complications of fluoroscopically guided interlaminar cervical epidural injections have been reported to be much less frequent and major complications are extremely rare (80-84,86). The safety of interlaminar epidurals may be due to vulnerable arteries and ischemic neurologic injuries after transforaminal epidural injections (85). Huston (84) reviewed both interlaminar and transforaminal epidural injections in the cervical region. Even though the prevalence of dural puncture is higher with interlaminar epidural injections, other major complications are less stout (84). A review of epidural steroid injections (83) for cervical radiculopathy concluded that there was greater risk of major and devastating complications with cervical transforaminal epidural injections compared to interlaminar epidural steroid injections related to the risk of arterial puncture and injection.

In a national survey of technical aspects of epidural steroid injections Cluff et al (87) reported that only 39% of interlaminar epidural injections were performed under fluoroscopy in academic settings compared to 73% in private practice settings. Stojanovic et al (88) evaluated the role of fluoroscopy in cervical epidural steroid injections. They found a 53% rate of lose of resistance during the first attempt to enter the epidural space. Unilateral epidural contrast spread was found in 51% and ventral epidural spread was found in 28% of cases. The average number of cervical vertebral levels covered with 2 mL of contrast was 3.14, with significantly wider spread noted in those patients who had not had undergone previous cervical laminectomy. Multiple authors (88-90) studied epidurography contrast patterns. Kim et al (89) performed all epidural injections at C6-C7 levels with epidurography with injection of 1, 2, or 3 mL of contrast. The rate of ventral epidural spread of 56.7% in Group A with 1 mL of injection, 90% in Group B with 2 mL of contrast, and 93.3% in Group C with 3 mL of contrast. They concluded that 2 mL of contrast injection was optimal. Goel and Pollan (90), in their study with cervical epidural steroid injections performed in the midline at C6-C7 and C7-T1, found the contrast consistently covered the dorsal cervical epidural space bilaterally, irrespective of the volume used or neck flexion angle used. Goodman et al (91) described optimizing patient positioning and fluoroscopic imaging for the performance of cervical interlaminar epidural steroid injections. Compared to the lumbar spine, in the cervical spine, the epidural space is smaller (92,93). In addition, there is also reported to be a higher incidence of discontinuity in the ligamentum flavum. Consequently, both of these factors can result in a higher rate of dural puncture during cervical interlaminar epidural injections, which can lead to rare but potentially serious complications (92,93).

There have been 2 systematic reviews (70,94), multiple guidelines (2), a Cochrane review of medicinal and injection therapies for mechanical neck disorders (7), and a document reassessing the evidence of the American College of Occupational and Environmental Medicine (ACOEM) guidelines (95) that included analysis of cervical epidural injections. However, the evidence for cervical interlaminar epidural injections has been a subject of debate and at best has had only moderate success in managing cervical radiculopathy, while there was no evidence available in the management of axial or discogenic neck pain, spinal stenosis, or postsurgery syndrome at the time of these evaluations.

Benyamin et al (70) in a systematic review of the effectiveness of cervical epidurals in the management of chronic neck pain illustrated moderate evidence for cervical epidurals in the management of chronic neck and upper extremity pain.

Recent publications of epidural injections utilizing fluoroscopy also provide the basis for emerging literature on the effectiveness of cervical epidural injections. Thus, the purpose of this systematic review is to evaluate cervical epidural injections with or without steroids in the management of chronic neck pain and upper extremity pain.

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 (2,96-104), Consolidated Standards of Reporting Trials (CONSORT) guidelines for the conduct of randomized trials (105-108), Standards for Reporting Observational Studies (STROBE) (109), Cochrane guidelines (96,101,102), Chou and Huffman's guidelines (110), and quality of reporting of analysis (98).

1.1 Criteria for Considering Studies for This Review

1.1.1 Types of Studies

Randomized controlled trials (RCTs)
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 neck and/or upper extremity pain of at least 3 months duration.

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

1.1.3 Types of Interventions

The interventions were cervical interlaminar epidural injections appropriately performed with proper technique preferably under fluoroscopic or CT guidance.

1.1.4 Types of Outcome Measures

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

1.2 Literature Search

Searches were performed from the following sources without language restrictions:

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

The search period was from 1966 through December 2011.

1.3 Search Strategy

The search strategy emphasized chronic neck and upper extremity pain, disc herniation, discogenic pain, post cervical surgery syndrome, cervical spinal stenosis, and radiculitis or radiculopathy treated with cervical interlaminar epidural injections.

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

1.4 Data Collection and Analysis

The review focused on randomized trials, observational studies, and reports of complications. The population of interest was patients suffering with chronic neck and upper extremity pain for at least 3 months. Only cervical interlaminar epidural injections with or without steroids were evaluated. All of the studies providing appropriate management and with outcome evaluations of one month or longer and statistical evaluations were reviewed. Reports without appropriate diagnosis, non-systematic reviews, book chapters, and case reports 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) (100,111). 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

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

The methodological qualities 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) (101) for randomized trials and Newcastle-Ottawa

Table 1. ***Clinical relevance questions.***

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

Scoring adapted and modified from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. *Cochrane Database Syst Rev* 2008; 3:CD001824 (111).

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

A	1. Was the method of randomization adequate?	A random (unpredictable) assignment sequence. Examples of adequate methods are coin toss (for studies with 2 groups), rolling a die (for studies with 2 or more groups), drawing of balls of different colors, drawing of ballots with the study group labels from a dark bag, computer-generated random sequence, pre-ordered sealed envelopes, sequentially ordered vials, telephone call to a central office, and pre-ordered list of treatment assignments. Examples of inadequate methods are alternation, birth date, social insurance/security number, date in which they are invited to participate in the study, and hospital registration number.	Yes/No/ Unsure
B	2. Was the treatment allocation concealed?	Assignment generated by an independent person not responsible for determining the eligibility of the patients. This person has no information about the persons included in the trial and has no influence on the assignment sequence or on the decision about eligibility of the patient.	Yes/No/ Unsure
C	Was knowledge of the allocated interventions adequately prevented during the study?		
	3. Was the patient blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the patients or if the success of blinding was tested among the patients and it was successful.	Yes/No/ Unsure
	4. Was the care provider blinded to the intervention?	This item should be scored "yes" if the index and control groups are indistinguishable for the care providers or if the success of blinding was tested among the care providers and it was successful.	Yes/No/ Unsure

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

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

Adapted and modified from Furlan AD, et al; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. Spine (Phila Pa 1976) 2009; 34:1929-1941 (101).

Scale for observational studies (Tables 3 and 4) (112). For nonrandomized observational studies, the patient population should have had at least 50 total or at least 25 in each group if they were comparison groups.

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

For adverse effects, confounding factors, etc., it

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

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

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

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (112).

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

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

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

Wells GA, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analysis. www.ohri.ca/programs/clinical_epidemiology/oxford.asp (112).

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 cervical interlaminar epidural injections will also be 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 planned 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 (113). Combined results with I2 > 50% were considered substantially heterogenous.

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

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

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

Qualitative (the direction of a treatment effect) and quantitative (the magnitude of a treatment effect) conclusions were evaluated. Random-effects meta-analysis to pool data was also used (114).

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 (115), chronic musculoskeletal pain (116), and chronic low back pain (97,98,100,103,117,118), which have been commonly utilized. Recently robust measures with ≥ 50% change in pain relief and/or functional status have been published (119-140). Consequently, for this analysis, we utilized 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 (i.e., disc herniation, axial discogenic pain, spinal stenosis, or postsurgery syndrome). 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 (141).

1.5 Summary Measures

Summary measures included 50% or more reduction of pain or at least a 3 point decrease in pain scores in at least 40% of the patients, 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 (142) as illustrated in Table 5, criteria which has been utilized by multiple authors (110,143-150).

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

Two of the review authors independently, in an unblinded standardized manner, analyzed the evidence. Any disagreements between reviewers were resolved by a third author and a consensus. If there were any conflicts of interest (e.g., authorship), those reviewers of those manuscripts did not participate in the assessment and analysis of those studies.

1.7 Outcome of the Studies

In the randomized trials, a study was judged to be positive if the cervical interlaminar epidural injection therapy was clinically relevant and effective, either with a placebo control or active control. This indicates that the difference in effect for the primary outcome measure is statistically significant on the conventional 5% level. In a negative study, no difference between

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

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

Adapted and modified from methods developed by U.S. Preventive Services Task Force (110,142).

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 fluoroscopic 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, axial or discogenic pain, spinal stenosis, and post-surgery syndrome).

2.0 Results

Figure 1 shows a flow diagram of study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (99). There were 34 studies considered for inclusion (130-135,151-178).

Of the 34 cervical interlaminar epidural trials identified (130-135,151-178), 24 studies were excluded (154-177). Table 6 shows the reasons for exclusion. Of these, none were randomized trials. There were 3 studies evaluating a transforaminal approach (159,167,173). One of the studies described injection technique under computed tomography (CT) (169). A study which was titled, "Epidural Steroid-Based Technique for Cervicogenic Headache Diagnosis" was not available for review (170).

Table 7 illustrates characteristics of studies considered for inclusion. There were 9 randomized trials (130-135,151-153) with 2 duplicate studies (130,131,134,135) meeting the inclusion criteria, thus there were a total of 7 trials evaluating various conditions. Only one study by Pasqualucci (153) was a follow-up of 6 months. All other studies included one year follow-up. There were no non-randomized or observational studies meeting the inclusion criteria.

2.1 Clinical Relevance

Of the 7 trials assessed for clinical relevance, all of them met criteria with score of 3 of 5 or greater (130-135,151-153). Table 8 illustrates 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 6 randomized trials (after combining duplicates) evaluating long-term response of 6 months or longer (130-135,151,152) with one study (153) with a follow-up of 6 months. Four trials were considered high quality (130-135) and 3 trials were considered moderate quality (151-153).

Of the included condition-specific studies, 4 trials included patients with disc herniation (130,134,151-153), one trial included patients with disc-related axial pain without disc herniation or radiculitis (131,135), one trial included patients with spinal stenosis (132), and one trial included patients with post surgery syndrome (133).

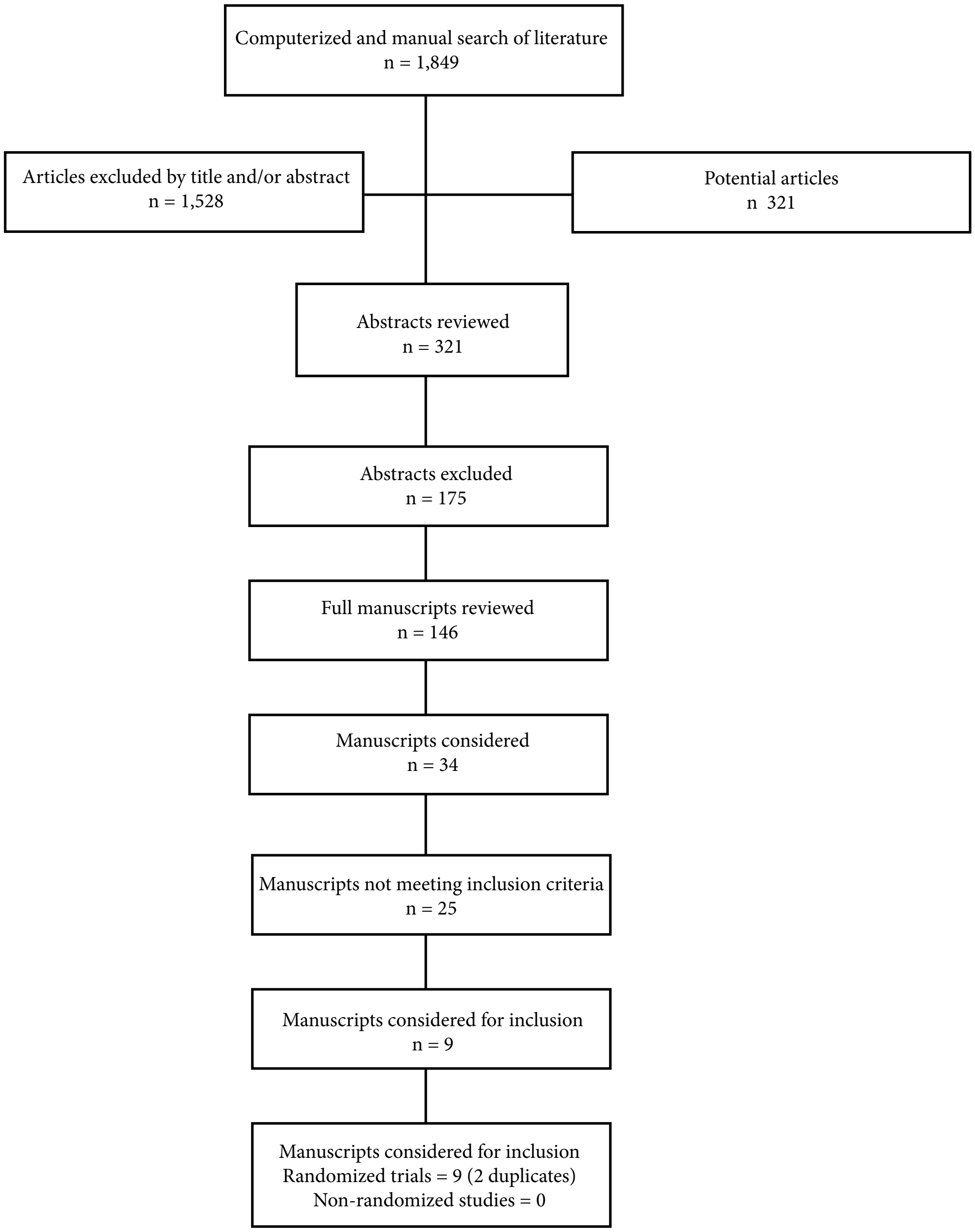

Fig. 1. ***The flow diagram illustrating published literature evaluating cervical interlaminar epidural injections.***

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)
NON-RANDOMIZED				
Rowlingson & Kirschenbaum (154)	Cervical radiculitis	25	15.1 months	Blind retrospective evaluation in 25 patients.
Ferrante et al (155)	Neck pain and cervical radiculopathy	100	NA	Blind cervical interlaminar epidural injections with 26% cervical spondylosis, 6% spinal stenosis, 36% herniated disc, and no MRI abnormalities in 32%.
Grenier et al (156)	Chronic cervicobrachial neuralgia	29	24 months	Blind technique in 29 patients.
Proano et al (157)	Cervical disc herniation	93	16 months	Blind procedure with the ability to follow only two-thirds of the patients.
Cicala et al (158)	Neck and upper extremity pain	57	6 months	Blind cervical epidural injections in 58 patients including 16 assigned to acute cervical myofascial strain, including patients with spondylosis = 25, strain = 16, and all other conditions = 17.
Shakir et al (159)	Cervical radicular pain	79	NA	Retrospective evaluation with transforaminal approach.
Kirpalani & Mitra (160)	Cervical radiculopathy	22	NA	Authors evaluated in a long retrospective chart review of only 22 patients with chronic opioid use.
Nawani et al (161)	Cervical and lumbosacral radiculopathies	50	6 weeks	A total of 50 patients with cervical and lumbar radiculopathy utilizing a blind technique.
Fish et al (162)	Cervical radiculopathy	32	NA	A retrospective evaluation of 32 patients involving disc herniation, nerve root compromise, neural foraminal stenosis, and central canal stenosis.
Lasbleiz et al (163)	Mechanical cervicobrachial neuralgia	34	90 days	A small study performed with CT-guided epidural injections also including 34 patients.
Dirksen et al (164)	Reflex sympathetic dystrophy	1	NA	One blind epidural for reflex sympathetic dystrophy.
Strub et al (165)	Neck pain or cervical radicular pain	161	10 days	A large study evaluating short-term results on factors influencing outcome with a 10-day follow up.
Kwon et al (166)	Neck pain and cervical radiculopathy	76	2 weeks	Even though study is fluoroscopically directed, it was of a short-term follow-up evaluating prognostic factors.
Lin et al (167)	Cervical disc herniation	70	13 months	All cervical epidural steroid injections were administered by transforaminal route.
Dougherty et al (168)	Cervical radiculopathy	20	One year	This study included fluoroscopic cervical epidural injections in conjunction with spinal manipulation, however in only 20 patients.
Morcet et al (169)	Cervicobrachial neuralgia	NA	NA	Technical description.
Martelletti et al (170)	Cervicogenic headache diagnosis	NA	NA	Appears to be technical description. The manuscript was not available for review.

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)
Pawl et al (171)	Cervical discogenic spondylosis	103	18 months	The study was performed blindly and the analysis was retrospective.
Mangar & Thomas (172)	Cervical pain syndrome	80	NA	Injections were performed with a blind approach.
Lee et al (173)	Cervical disc herniation	159	One month	Authors studied cervical transforaminal epidural steroids injection for the management of cervical radiculopathy for comparison of particulate versus non-particulate steroids.
Bush & Hillier (174)	Cervical radiculopathy	68	7 months	Even though the study was performed under fluoroscopy, the average duration of pain was only 2 months, thus failing to meet the inclusion criteria.
Shulman (175)	Neck pain	155	NA	A large number of patients with multiple injections, in a retrospective short review, but performed with a blind technique with multiple categories among them.
Warfield et al (176)	Cervical radiculitis	16	One year	A small number of patients with a blind approach.
Catchlove & Braha (177)	Chronic head and neck pain	45	NA	A retrospective evaluation performed blindly in 45 patients.

2.3 Meta-Analysis

All randomized trials were evaluated for homogeneity for inclusion in the meta-analysis. There were no true placebo controlled trials and there was only one study which was described as placebo controlled, despite its active control design (152). Among the active controlled trials, there were 4 trials evaluating cervical disc herniation (130,134,151-153), one trial evaluating disc related axial pain without disc herniation (131,135), one trial evaluating central spinal stenosis (132), and another trial evaluating the effectiveness of post surgery syndrome (133). Consequently no meta-analysis was feasible.

2.4 Study Characteristics

Table 10 illustrates the study characteristics of the included studies.

2.5 Analysis of Evidence

The evidence was synthesized based on the specific condition for which the cervical interlaminar epidural injection was provided. Table 10 illustrates the results of randomized trials of the effectiveness of cervical interlaminar epidural injections in managing disc herniation or radiculitis, axial or discogenic pain, central spinal stenosis, and postsurgery syndrome.

2.5.1 Disc Herniation and Radiculitis

There were a total of 4 studies meeting the inclusion criteria evaluating cervical interlaminar epidural injections in managing disc herniation or radiculitis (130,134,151-153). There was only one high quality randomized trial performed with an active control design under fluoroscopic evaluation (130,134). Two of the other 3 studies were performed blindly (151,152), one described as a placebo control design, though the control group received steroids (152). The second study utilized morphine as an additive to the solution (151). Finally, the last study (153) compared continuous versus single epidural injections providing up to approximately 8 injections in the single group and assessed only 6 month pain relief. The quality of these 3 studies performed without fluoroscopy was moderate.

Among all the randomized trials, only one study utilized 120 participants with 60 patients in each group,

Table 7. *Assessment of randomized trials of cervical interlaminar epidural 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					
Manchikanti et al (130,134)	R, AC, F	X				120 Local anesthetic only = 60 Local anesthetic with steroids = 60	Cervical epidural injection with local anesthetic 0.5%, 5 mL or with local anesthetic 0.5%, 4 mL with 6 mg (1 mL) of non-particulate Celestone Number of injections = 1 to 4	One year	Significant improvement > 50% pain relief and > 50% functional status improvement	Authors concluded that cervical interlaminar epidural injections with local anesthetic with or without steroids might be effective in 77% with local anesthetic or 82% with steroids in the successful group. This is an active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.
Manchikanti et al (131,135)	R, AC, F		X			120 Local anesthetic only = 60 Local anesthetic with steroids = 60	Cervical epidural injection with local anesthetic 0.5%, 5 mL or with local anesthetic 0.5%, 4 mL with 6 mg (1 mL) of non-particulate Celestone Number of injections = 1 to 4	One year	Significant improvement > 50% pain relief and > 50% functional status improvement	Authors concluded that cervical interlaminar epidural injections with local anesthetic with or without steroids might be effective in 78% in local anesthetic group and 73% in steroid group. This is an active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.
Manchikanti et al (132)	R, AC, F			X		60 Local anesthetic only = 30 Local anesthetic with steroids = 30	Cervical epidural injection with local anesthetic 0.5%, 5 mL or with local anesthetic 0.5%, 4 mL with 6 mg (1 mL) of non-particulate Celestone Number of injections = 1 to 4	One year	Significant improvement > 50% pain relief and > 50% functional status improvement	This is an active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques. Significant pain relief was seen in 87% in both groups, while in Group I, 77% and in Group II, 87% had functional status improvement.
Manchikanti et al (133)	R, AC, F				X	56 Local anesthetic only = 28 Local anesthetic with steroids = 28	Cervical epidural injection with local anesthetic 0.5%, 5 mL or with local anesthetic 0.5%, 4 mL with 6 mg (1 mL) of non-particulate Celestone. Number of injections= 1 to 4	One year	Significant improvement > 50% pain relief and > 50% functional status improvement	This is an active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques. Significant pain relief was seen in 71% in Group I, and 68% in Group II. Functional status improvement was 71% in Group I and 64% in Group II.

Table 7 (cont.). *Assessment of randomized trials of cervical interlaminar epidural 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					
Castagnera et al (151)	R, AC, B	X				24	Steroid group received in 14, 0.5% Lidocaine plus triamcinolone acetonide 10 mg per mL. The steroid plus morphine group received in 10, the same combination plus 2.5 mg of morphine sulfate Number of injections=1	One year	Pain relief, VAS, work status	Success rate was 78.5% in the steroid group and 80% in the group with steroids and morphine. Pain relief remained stable with time with long-term follow-up of as much as 48 months with mean of 43 ± 18.1 months. Results suggested that a single cervical epidural steroid injection performed produces long-lasting pain relief which is not improved when morphine is combined with steroids.
Stav et al (152)	R, AC, B	X				42	One group treated with cervical epidural steroid/lidocaine injections and other treated with steroid/ lidocaine injections into the posterior neck muscles. Number of injections=1 to 3	One year	Pain relief, change in range of motion, reduction of daily dose of analgesics, return to work.	Authors concluded significant effectiveness. The results illustrated that one year after the treatment, 68% of the patients receiving epidural steroid injections had very good and good pain relief, whereas only 11.8% of group patients with intramuscular injections showed improvement. This is a well-performed randomized active-control study, even though it was performed without fluoroscopy.
Pasqualucci et al (153)	R, AC, B	X				40 of 160	Patients received a single injection with 0.25% bupivacaine with epinephrine 1 in 200,000 in a volume of 6 mL with 80 mg of methylprednisolone acetate every 4-5 days to a maximum of 8 blocks. Continuous epidural group patients received catheterization with repeat injection 12-24 hours and steroids 4-5 days.	6 months	Pain control of greater than 80%, pain-free hours of sleep	There was significant decrease in pain control and increase of pain-free sleep with single as well as continued administrations in approximately 17 of 20 patients with single injection and 17 of 20 patients with continuous infusion at one month and 6 months.

R = Randomized. AC = Active-Control. F = Fluoroscopy . B=Blind. VAS = Visual Analog Scale

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
Manchikanti et al (130,134)	+	+	+	+	+	5/5
Manchikanti et al (131,135)	+	+	+	+	+	5/5
Manchikanti et al (132)	+	+	+	+	+	5/5
Manchikanti et al (133)	+	+	+	+	+	5/5
Castagnera et al (153)	+	+	+	-	+	4/5
Stav et al (152)	+	+	+	-	+	4/5
Pasqualucci et al (153)	+	+	+	-	-	3/5

+ = positive; - = negative ; U = unclear

Scoring adapted from Staal JB, et al. Injection therapy for subacute and chronic low-back pain. Cochrane Database Syst Rev 2008; 3:CD001824 (111).

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

	Manchikanti et al (130,134)	Manchikanti et al (131,135)	Manchikanti et al (132)	Manchikanti et al (133)	Castagnera et al (151)	Stav et al (152)	Pasqualucci et al (153)
Randomization adequate	Y	Y	Y	Y	U	N	N
Concealed treatment allocation	Y	Y	Y	Y	U	N	N
Patient blinded	Y	Y	Y	Y	U	N	N
Care provider blinded	Y	Y	Y	Y	U	N	N
Outcome assessor blinded	N	N	N	N	U	N	N
Drop-out rate described	Y	Y	Y	Y	Y	Y	Y
All randomized participants analyzed in the group	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
Groups similar at baseline regarding most important prognostic indicators	Y	N	N	N	Y	Y	Y
Co-interventions avoided or similar	Y	Y	Y	Y	Y	Y	Y
Compliance acceptable in all groups	Y	Y	Y	Y	Y	Y	Y
Time of outcome assessment in all groups similar	Y	Y	Y	Y	Y	Y	Y
Score	11/12	10/12	10/12	10/12	7/12	7/12	7/12

Y=yes; N=no; U=unclear

Table 10. ***Results of randomized trials of effectiveness of cervical interlaminar epidural injections.***

Study	Study Characteristics	Methodological Quality Scoring	Participants	Interventions	Pain Relief and Function			Results									Comment(s)
								Short-term ≤ 6 mos.			Long-term						
											> 6 mos.			1 year			
					3 mos.	6 mos.	12 mos.	ST	LA	SAL	ST	LA	SAL	ST	LA	SAL	
DISC HERNIATION AND RADICULITIS																	
Manchikanti et al (130,134)	R, AC, F	11/12	120 local anesthetic= 60 Local anesthetic with steroids = 60	Local anesthetic or with Celestone Number of injections = 1 to 4	83% vs. 70%	82% vs. 73%	72% vs. 68%	P	P	NA	P	P	NA	P	P	NA	Positive large study.
Castagnera et al (151)	R, AC, B	7/12	24	local anesthetic with steroid or steroid plus morphine Number of injections=1	79.2%	79.2%	79.2%	P	NA	NA	P	N	NA	P	NA	NA	A small study with positive results
Stav et al (152)	R, AC, B	7/12	42	local anesthetic with steroid or IM steroid Number of injections=1 to 3	NA	NA	68% vs.11.8%	NA	NA	NA	NA	NA	NA	P	NA	NA	A small study showing satisfactory improvement
Pasqualucci et al (153)	R, AC, B	7/12	40 of 160	Bupivacaine with methylprednisolone acetate	NA	Single vs. continuous 58.5%, 73.7% improvement	NA	NA	NA	NA	P	NA	NA	NA	NA	NA	Small study with positive results
DISCOGENIC PAIN																	
Manchikanti et al (131,135)	R, AC, F	10/12	120	Local anesthetic or with Celestone	68% vs. 77%	67% vs. 73%	72% vs. 68%	P	P	NA	P	P	NA	P	P	NA	Positive results
SPINAL STENOSIS																	
Manchikanti et al (132)	R, AC, F	10/12	60	Local anesthetic or with Celestone	77% vs. 87%	87% vs. 80%	73% vs. 70%	P	P	NA	P	P	NA	P	P	NA	Positive results
POST SURGERY SYNDROME																	
Manchikanti et al (133)	R, AC, F	10/12	56	Local anesthetic or with Celestone	68% vs. 68%	64% vs. 71%	71% vs. 64%	P	P	NA	P	P	NA	P	P	NA	Positive results

R = Randomized; AC = Active-Control; F = Fluoroscopy; B=Blind; VAS = Visual Analog Scale; P = positive; N = negative; NA = not applicable either with local anesthetic or local anesthetic with steroids.

All the studies showed significant improvement compared to baseline, while there was no significant improvement among the groups, except in the study by Stav et al (152) utilizing intramuscular steroid injection. However, this study included only a small proportion of patients and provided only one injection. These results have not been replicated with improvement in a significant proportion of patients with only one epidural injection. The largest randomized trial by Manchikanti et al (130,134) showed significant improvement from the baseline at all levels, including function as well as disability. Of the 4 randomized trials meeting the inclusion criteria evaluating cervical interlaminar epidural injections, all of them showed positive results for the long-term; however, the results were strong in only one study (130,134).

2.5.2 Axial or Discogenic Pain

There was only one study evaluating axial discogenic pain, the role of cervical interlaminar epidural injections, in patients without disc herniation, radiculitis, or facet joint arthropathy (131,135). This study showed positive results. This was a large study performed in a contemporary interventional management practice setting utilizing an active control design with 60 patients in each group.

This study showed positive results at all levels whether local anesthetic was utilized alone or combined with steroids, both in pain relief as well as functional status.

2.5.3 Spinal Stenosis

There was only one randomized trial meeting the inclusion criteria in the evaluation of central spinal stenosis in the cervical spine (132). This study was of an active control design and a preliminary report, but showed positive results.

2.5.4 Postsurgery Syndrome

There was only one randomized trial evaluating the effectiveness of cervical interlaminar epidural injections in post surgery syndrome with or without steroids with an active control design, but with preliminary results (133). The results were positive at 3, 6, and 12 months both for pain and functional status with or without steroids.

2.6 Level of Evidence

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

2.6.1 Cervical Disc Herniation

For cervical disc herniation with radiculitis, based on one large fluoroscopically directed active control study with or without local anesthetic with steroids (130,134), in conjunction with 3 smaller randomized trials with positive results (151-153), the evidence is good.

Cervical epidural with local anesthetic only is supported by one randomized, fluoroscopically directed trial with 120 patients, showing positive results. However, due to the nature of only one study, the evidence is considered as fair.

2.6.2 Axial or Discogenic Pain

There was only one study evaluating the results of cervical discogenic or axial pain (131,135), which showed positive results in 120 patients, thus, the level of evidence is fair.

2.6.3 Spinal Stenosis

There was only one study evaluating the results of spinal stenosis (132), which showed positive results in 60 patients, thus, the level of evidence is fair.

2.6.4 Post Surgery Syndrome

There was only one study evaluating the results of post surgery syndrome (133), which showed positive results in 56 patients, thus, the level of evidence is fair.

2.6.5 Summary of Evidence

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

3.0 Complications

Serious complications of cervical interlaminar epidural procedures include spinal cord trauma, spinal cord or epidural hematoma formation, nerve injury, subdural or subarachnoid injection, intravascular entry either venous or arterial, vascular injury or vascular embolism, and injection leading to abscess, even though serious complications are rarely seen

(70,75,77-85,94,179-226). Multiple minor side effects include increase in the neck pain, vasovagal reactions, headache, insomnia, increase in temperature, and dural puncture.

Manchikanti et al (86) evaluated complications and side effects of epidural injections. Among these, 2,376 were performed in the cervical region with an interlaminar approach. The results illustrated intravascular entry in 4.2%, return of blood in 1.2%, profuse bleeding in 0.7%, bruising in 0.3%, vasovagal reaction in 0.04%, transient nerve root irritation in 0.25%, transient spinal cord irritation in 0.21%, dural puncture in 1%, postlumbar puncture headache in 0.08%, and facial flushing in 0.08%.

4.0 Discussion

This systematic review evaluating the effectiveness of cervical interlaminar epidural injections in managing chronic neck pain and upper extremity pain caused by disc herniation with radiculitis showed good evidence for cervical interlaminar epidural injections with local anesthetic and steroids. This evaluation also showed fair evidence for cervical epidural with local anesthetic only in managing disc herniation and radiculitis due to the fact that there was only one study (130,134). The evaluation of disc herniation and radiculitis was included in 4 randomized trials, one of them being a large randomized, double-blind, active control trial in a contemporary interventional pain management practice. The evidence for axial neck pain or cervical discogenic pain is fair based on a single randomized, double-blind, active controlled trial with or without steroids with strong measures of outcome. The evidence is fair for central spinal stenosis and post surgery syndrome based on one manuscript for each condition with publication of only preliminary results. In this evaluation, a total of 7 randomized trials met the inclusion criteria. The remaining studies were all performed without fluoroscopic utilization blindly and were either retrospective or prospective – but, observational.

The previous systematic review by Benyamin et al (70) showed Level II-I evidence for cervical interlaminar epidural injections with steroids for patients with chronic neck and upper extremity pain based on a plurality of 3 studies. However, none of these studies were performed under fluoroscopy and none of the studies had more than 100 patients to be studied. In contrast, the present evaluation shows an additional 4 randomized trials, 2 of them with a large proportion of patients, while 2 were only preliminary, performed in a contemporary interventional pain management practice, after failure of conservative management, under fluoroscopy, based on specific disorders including disc herniation, axial or discogenic pain, central spinal stenosis, and post surgery syndrome. Compared to the studies of caudal and lumbar epidural injections, trials or studies of cervical epidural injections are rare.

Cervical epidural steroid injections have been studied since 1985 (171). Historically, cervical epidural steroid injections originated from Pagés description of needle placement into the lumbar epidural space based on obstruction of free flow of spinal fluid from the needle and lack of resistance to injection of local anesthetic in 1921 (200). Dogliotti (201) was the first to describe the technique of cervical epidural block and also the first to describe, in 1933, the loss of resistance technique. The underlying mechanism of action of epidurally administered steroid and local anesthetic injection is still not well understood. A common problem encountered with any epidural injection is inaccurate needle placement, leading to inaccurate placement of the injectate (2,94,202). Consequently, proponents for fluoroscopic guidance in epidural steroid injections advocate utilizing this technique in order to assure that medications reach the appropriate and desired intervertebral space (202). In a study of 38 interlaminar cervical epidural steroid injections, they (202) found a 53% rate of false loss of resistance during the first attempt to enter the epidural space. They suggested using fluoroscopy can improve the accuracy of needle placement and medication delivery. Even with second and third attempts, the success rate improved only to 75% with loss of resistance technique without fluoroscopy (88). In addition, it was also shown that when cervical epidural steroid injections are performed in the midline at C6/7 and C7/T1 under fluoroscopy, the contrast consistently covers the dorsal cervical epidural space bilaterally, irrespective of the volume used or neck flexion angle used (90). Further, fluoroscopic guidance also helps to avoid potential intravascular injections (203). Fluoroscopic utilization with contrast injection will also delineate multiple filling patterns including subdural and subarachnoid patterns. Even though the underlying mechanism of action of epidurally administered steroid and local anesthetic is not well understood, it is believed that the achieved neural blockade alters or interrupts nociceptive input, reflex mechanism of the afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities (2,94,178,188,202). 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 (153,178-188,227-240). The emerging evidence also shows that the long-lasting effect may be obtained with local anesthetics with or without steroids (122,241-259). Further, it has been shown in rat experiments that nerve root infiltration prevented mechanical allodynia, even though no additional benefit from using corticosteroid was identified (240). Thus, it is suggested that corticosteroid may be unnecessary for nerve root blocks; in fact, this concept has been reinforced by numerous randomized and observational studies (122,252,254,257-268). Finally, in evaluation of epidural local anesthetic plus corticosteroid for the treatment of cervical brachial radicular pain with either a single injection or a continuous infusion (153), continuous epidural showed better control of chronic cervicobrachial pain compared with single injection, even though a corticosteroid was utilized in both injections. Thus, local anesthetic provides an independent effect or an additive effect.

Multiple studies have evaluated prognostic factors for cervical epidural injections including the duration of pain. One retrospective evaluation (160) also evaluated the influence of chronic opioid use as a negative predictive factor for response to cervical steroid injections. This small study of 22 patients with cervical radiculopathy in a retrospective evaluation illustrated a significant difference with opioid-naïve patients receiving better relief in the short-term than the patients on chronic opioid therapy (70% vs. 20%). Fish et al (162) evaluated the MRI prediction of therapeutic response to epidural steroid injections in patients with cervical radiculopathy and concluded that patients with central canal stenosis achieved a significantly better functional outcome after cervical epidural steroid injections than those without. Thus, they believed that the MRI finding of central canal stenosis is a potential indication for the cervical epidural injections. Strub et al (165) evaluated factors influencing the outcomes in the short-term in 161 patients with 280 interlaminar epidural injections. They also showed that patients who required narcotics for their symptoms before the procedure showed poor pain relief. However, in the modern era, the majority of the patients with chronic pain have received extensive opioid therapy prior to presenting to interventional pain management settings. The positive results illustrated in recent active controlled trials (130-135) shows that even though there are changes in opioid intake, most patients continue to be on opioids, thus the difference illustrated in the above studies (158-165) has not been replicated in long-term studies, rather the results are different from these reports (130-135). One retrospective evaluation also showed manipulation after cervical epidural injection was effective (168). Kwon et al (166) in a short-term evaluation assessed the prognostic factors in a non-randomized fluoroscopically directed study in 76 patients. In the short-term, they concluded that the patients with herniated discs had significantly better results than patients with spinal stenosis. They also showed other non-significant predictors of an improved outcome including a symptom duration of less than 6 months, a young age, and the presence of cervical radiculopathy. Ferrante et al (155) reviewed 100 patients and attempted to classify predictors of therapeutic outcomes after cervical epidural steroid injections. They separated patients into 5 clinical groups with radiculopathy with structural abnormality, radiculopathy without structural abnormality, radiculitis with structural abnormality, radiculitis without structural abnormality, and cervical spondylosis. They also assessed symptoms and signs. They concluded that the presence of radicular pain predicted a better outcome, a radiologic diagnosis abnormality or herniated disc predicted a poor outcome. A multitude of other predictors they attempted to evaluate were non-significant, thus, these predictors are extremely confusing. Overall, the recent studies illustrated that (130-135) the results are superior in patients with disc herniation and/or radiculitis or axial discogenic pain after facet joint pain has been ruled out.

The limitations of this review include a paucity of literature specifically with proper design and utilization of fluoroscopy. Even though criticism has been offered for lack of placebo controlled trials, they are unrealistic in interventional pain management. Further, it also has been significantly misinterpreted (269-271). Some authors also have mistakenly reported that any local anesthetic injection which yields similar results as steroids or another agent is considered a placebo. The experimental and clinical findings from investigations, electrophysiological effects, and muscle activation have shown differing results illustrating that there is no true placebo effect (268,272-275). However, the literature also has shown that appropriate design of placebo has in fact shown negative results (276-278).

The results of this systematic review may be applied in interventional pain management practices utilizing appropriate evaluations. We found only 7 articles were identified which met the inclusion criteria

(130-135,151-153). In conclusion, the results of this systematic review have significant implications for clinical practices in interventional pain management. Appropriately performed interventions are illustrated to be effective based on the results of this systematic review.

5.0 Conclusion

Review of 7 manuscripts meeting inclusion criteria showed good evidence for radiculitis secondary to disc herniation with local anesthetics and steroids, fair evidence with local anesthetic only; whereas, the evidence is fair for local anesthetics, with or without steroids, for axial or discogenic pain, pain of central spinal stenosis, and pain of post surgery syndrome.

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