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Systematic Review

Do Cervical Epidural Injections Provide Long-Term Relief in Neck and Upper Extremity Pain? A Systematic Review

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Background: The high prevalence of chronic persistent neck pain not only leads to disability but also has a significant economic, societal, and health impact. Among multiple modalities of treatments prescribed in the management of neck and upper extremity pain, surgical, interventional and conservative modalities have been described. Cervical epidural injections are also common modalities of treatments provided in managing neck and upper extremity pain. They are administered by either an interlaminar approach or transforaminal approach.

Objectives: To determine the long-term efficacy of cervical interlaminar and transforaminal epidural injections in the treatment of cervical disc herniation, spinal stenosis, discogenic pain without facet joint pain, and post surgery syndrome.

Methods: The literature search was performed from 1966 to October 2014 utilizing data from PubMed, Cochrane Library, US National Guideline Clearinghouse, previous systematic reviews, and cross-references.

The evidence was assessed based on best evidence synthesis with Level I to Level V.

Results: There were 7 manuscripts meeting inclusion criteria. Of these, 4 assessed the role of interlaminar epidural injections for managing disc herniation or radiculitis, and 3 assessed these injections for managing central spinal stenosis, discogenic pain without facet joint pain, and post surgery syndrome. There were 4 high quality manuscripts. A qualitative synthesis of evidence showed there is Level II evidence for each etiology category. The evidence is based on one relevant, high quality trial supporting the efficacy of cervical interlaminar epidural injections for each particular etiology.

There were no randomized trials available assessing the efficacy of cervical transforaminal epidural injections.

Limitations: Paucity of available literature, specifically conditions other than disc herniation. Conclusion: This systematic review with qualitative best evidence synthesis shows Level II evidence for the efficacy of cervical interlaminar epidural injections with local anesthetic with or without steroids, based on at least one high-quality relevant randomized control trial in each category for disc herniation, discogenic pain without facet joint pain, central spinal stenosis, and post surgery syndrome.

Key words: Chronic neck pain, cervical disc herniation, cervical spinal stenosis, cervical post surgery syndrome, cervical discogenic pain, cervical epidural injections, interlaminar epidural injections, transforaminal epidural injections, steroids, local anesthetic

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Annual estimates of the prevalence of chronic neck pain in the general population of adults ranges from 12.1% to 71.5% with most estimates showing an annual prevalence between 30% and 50% with or without sprain or injury (1-7). Côté et al (7) described various grades of chronic neck pain with 5% of patients suffering from Grades III and IV neck pain, both of which are associated with high pain intensity and disability. Overall, they showed the prevalence and impact of neck pain on general health involving 15% of patients reporting Grade II-IV neck pain. Grade II has been defined as high pain intensity with few activity limitations (7). Similar to low back pain, neck pain is associated with significant economic, societal, and health impact (8-11). In fact, a report on the state of U.S. health from 1990 - 2010 describing the burden of diseases, injuries, and risk factors, showed low back pain as the number one disease leading to disability in 1990 and again in 2010, whereas neck pain ranked number 4 during the same period. In addition, chronic pain as a result of motor vehicle injuries has been shown to be present in 24% to 50% of those involved in motor vehicle injuries (6,12,13).

Neck and upper extremity pain with headache have been shown to be caused by intervertebral discs, cervical facet joints, ligaments, fascia, muscles, and nerve root dura which are capable of transmitting pain. Even though cervical radicular pain receives the most attention (6,14-21), multiple other mechanisms have been described as being responsible for neck and upper extremity pain. Prevalence studies of various structures causing neck and upper extremity pain show an annual incidence of cervical radicular pain of 83 per 100,000 population (17). The prevalence of facet joint pain based on controlled diagnostic blocks in patients with neck pain is 36% to 67% (6,22), and 16% to 20% for cervical discogenic pain (23). The pathogenesis of cervical radicular pain or discogenic pain has been linked to multiple chemicals including metalloproteinases, nitric oxide, interleukin-6, and prostaglandin E2 all of which are irritants of the spinal nerves causing inflammation (6,15,16,18,21). Cervical epidural injections are among the treatments described in managing neck and upper extremity pain of disc and nerve irritation without involvement of facet joints. Cervical epidural injections are performed utilizing either an interlaminar or transforaminal approach (6,19,20) and are one of the fastest growing modalities of interventional techniques in managing chronic neck pain and upper extremity pain (24-27).

The effectiveness of cervical epidural injections continues to be intensely debated, in particular for conditions other than disc herniation and radicular pain. Cervical transforaminal epidural injections or selective nerve root blocks are associated with high complication rates and intense debate (6,19,20,28-43). Complications with interlaminar epidural injections, though reported, are considered much less frequent or fatal compared to cervical transforaminal epidural injections. The important differences between interlaminar and transforaminal epidural injections include that while interlaminar entry delivers the medication close to the assumed site of pathology and the transforaminal approach is the target-specific modality requiring the smallest volume to reach the primary site of pathology and also leading to the site of pathology ventrally.

In addition, numerous complications described in recent years, such as fungal infections in compounded steroids leading to devastating complications (41) and the FDA warning on April 23, 2014 concerning injecting corticosteroids into the epidural space of the spine resulting in rare, but serious adverse events, have led to further controversy and discussions (42,43).

Multiple systematic reviews and guidelines performed by various groups of authors have reached different conclusions about the level of evidence for the effectiveness of cervical epidural injections in managing not only disc herniation and radiculitis, but also other conditions (6,19,20,44,45). Among the systematic reviews, Diwan et al (20) identified 34 studies assessing interlaminar epidural injections with the inclusion of 7 randomized trials in the analysis. They concluded that for cervical disc herniation the evidence was good, whereas for axial or discogenic pain, central spinal stenosis, and post surgery syndrome the evidence was fair. Other reviews were insufficient with multiple deficiencies.

Consequently, this systematic review was undertaken to determine the long-term efficacy of cervical interlaminar and transforaminal epidural injections in the treatment of disc herniation, spinal stenosis, discogenic pain without facet joint pain, and cervical post surgery syndrome. We utilized only randomized control trials (RCT), either placebo-controlled or active-controlled.

Methods

The methodology utilized in the systematic review followed the review process derived from evidence-based systematic reviews and meta-analysis of randomized trials (46,47).

The literature search was performed from 1966 to

October 2014 utilizing data from PubMed, Cochrane Library, US National Guideline Clearinghouse, previous systematic reviews, and cross-references.

Search Strategy

The search strategy emphasized disc herniation, radiculitis, radicular pain, cervicobrachialgia, spinal stenosis, discogenic pain, and post surgery syndrome in the cervical region or upper extremity pain treated with either interlaminar or transforaminal epidural injections. Search terminology was as follows:

((((((((((post laminectomy) OR post surgery pain) OR discogenic) OR spinal stenosis) OR radiculitis) OR radiculopathy) OR disc herniation) OR upper extremity) OR cervicobrachialgia)) AND (((transforaminal) OR interlaminar) OR epidural)) AND ((upper extremity) OR cervical) Filters: Humans

Inclusion Criteria

Only adults at least 18 years of age with chronic neck and upper extremity pain of at least 3 months duration were included. Furthermore, participants must have failed previous pharmacotherapy, exercise therapy, physical therapy, etc. prior to treatment with interventional pain management techniques. Only appropriately performed cervical epidural injections were included.

Outcome Measures

The primary outcome measure was pain relief and the secondary outcome measure was functional status improvement. Other aspects were also reviewed including psychological status, return to work, reduction or elimination of opioid use, other drugs, or other interventions; and complications.

All trials showing a 50% or more reduction of pain or at least a 3 point decrease in pain scores in at least 50% of patients were considered as providing efficacy.

Short-term improvement was considered as less than 6 months and long-term was considered as 6 months or longer.

Data Collection and Analysis

A uniform unblinded search strategy was applied. Studies with at least 3 months of outcome measures with appropriate statistical evaluations were reviewed.

At least 2 of the review authors independently, in an unblinded standardized manner, performed the literature search, analyzed the search data, and selected the trials for inclusion. A third author and consensus resolved any disagreements between reviewers.

Methodologic Quality or Risk of Bias Assessment

Methodological quality or risk of bias assessment of each individual manuscript was performed using Cochrane review criteria (Appendix 1) for RCTs (48) and interventional pain management quality and risk of bias assessment (Appendix 2) for RCTs (49). Cochrane review criteria have been utilized in a multitude of reviews. Recently, the American Society of Interventional Pain Physicians (ASIPP) developed a specific instrument for interventional techniques called Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment (IPM-QRB).

The quality of each individual article was independently assessed by 2 review authors who assessed the internal validity of all trials in an unblinded standardized manner. Any discrepancies between the 2 review authors were assessed by a third author and settled by consensus. Randomized trials meeting at least 4 of the 12 Cochrane review criteria or achieving a score of 20 of 48 on IPM-QRB criteria were utilized for analysis. Trials meeting 8 of 12 criteria on the Cochrane review or achieving a score of 32 of 48 on IPM-QRB were considered as high-quality trials. Trials meeting 4 to 7 criteria on Cochrane review or achieving a score of 20 to 31 on IPM-QRB were considered as moderate-quality trials; while studies meeting less than 4 criteria on Cochrane review or achieving a score less than 20 on IPM-QRB were considered as low quality.

Meta-analysis

If there were more than 2 homogenous studies in more than 2 trials of interlaminar or transforaminal injections in managing disc herniation and radiculitis, spinal stenosis, discogenic pain, or post surgery syndrome, meta-analysis was performed.

Analysis of Evidence

The analysis of evidence was performed based on ASIPP's grading of evidence (50) which was developed from Cochrane criteria of evidence synthesis and multiple other criteria including United States Preventive Services Task Force (USPSTF) analysis of evidence criteria as shown in Table 1.

Results

The results of the search criteria and selection of trials for inclusion in the systematic review are shown in a flow diagram of study selection as recommended by Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) (Fig. 1) (47).

Table 1. *ASIPP grading of evidence.*

Level I	Evidence obtained from multiple relevant high quality randomized controlled trials
Level II	Evidence obtained from at least one relevant high quality randomized controlled trial or multiple relevant moderate or low quality randomized controlled trials
Level III	Evidence obtained from at least one relevant moderate or low quality randomized controlled trial study or Evidence obtained from at least one relevant high quality non-randomized trial or observational study with multiple moderate or low quality observational studies
Level IV	Evidence obtained from multiple moderate or low quality relevant observational studies
Level V	Opinion or consensus of large group of clinicians and/or scientists.

Adapted and Modified from: Manchikanti L, Falco FJE, Benyamin RM, Kaye AD, Boswell MV, Hirsch JA. A modified approach to grading of evidence. *Pain Physician* 2014; 17:E319-E325 (50).

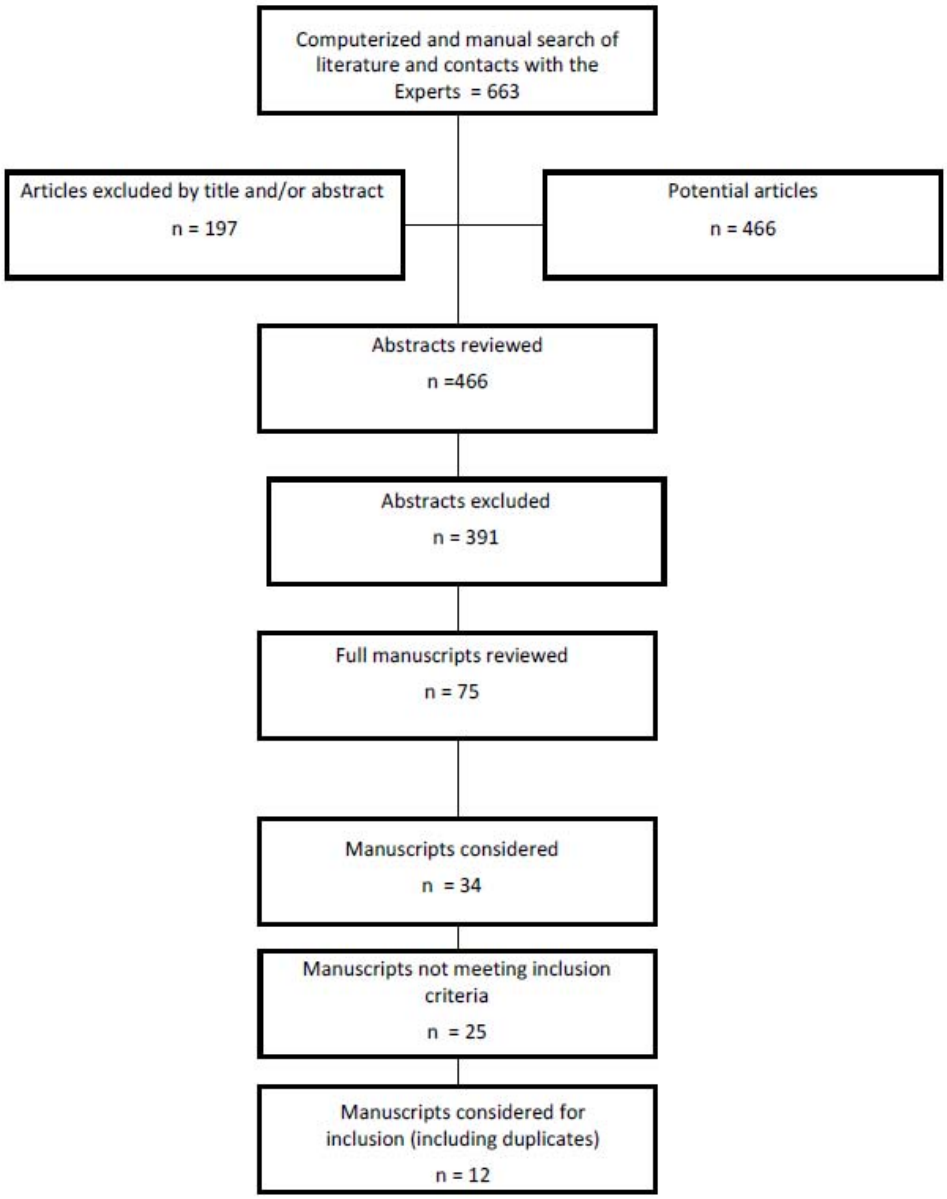

Fig. 1. *The flow diagram illustrating published literature evaluating cervical interlaminar and transforaminal epidural injections.*

Overall, there were 34 manuscripts considered for inclusion; however, only 7 randomized trials, either active-controlled or placebo-controlled met inclusion criteria (51-57). There were 3 RCTs assessing the transforaminal approach (58-60) which failed to meet the inclusion criteria.

Methodological Quality Assessment

A methodological quality assessment of all randomized trials meeting inclusion criteria was performed utilizing Cochrane review criteria as well as ASIPP's IPM-QRB instrument as shown in Tables 2 and 3. After combining duplicates, there were 6 randomized trials evaluating long-term response of 6 months or longer (51-56) with one trial (57) with a follow-up of less than 6 months. Four of the trials were considered as high quality (51-54) based on Cochrane review methodological criteria scores of over 8, as well as ASIPP's IPM-QRB assessment scores over 32. The other 3 trials were considered moderate quality with scores of 4 to 7 on Cochrane review criteria and 20 to 31 on ASIPP's IPM-QRB (55-57).

Characteristics of Included Trials

Of the 7 included trials of interlaminar epidural injections, 4 assessed patients with disc herniation (51,55-57), one trial included patients with disc related axial pain without disc herniation or radiculitis (52), one trial included patients with central spinal stenosis (53), and one trial assessed patients with post surgery syndrome (54). All of the trials were of an active control design. Only one trial had follow-up of less than 6 months (57). There were no true placebo-controlled trials. One trial did identify itself a placebo-controlled design utilizing intramuscular steroids in the control group (58). There were no trials of transforaminal epidural injections in the cervical spine meeting inclusion criteria for methodological quality assessment.

Study Characteristics

Table 4 describes study characteristics and results of RCTs of cervical interlaminar epidurals.

Disc Herniation and Radiculitis

A total of 4 studies met the inclusion criteria and evaluated the role of cervical interlaminar epidural injec-

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

	Manchikanti et al (51)	Manchikanti et al (52)	Manchikanti et al (53)	Manchikanti et al (54)	Castagnera et al (55)	Stav et al (56)	Pasqualucci et al (57)
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

Source: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976) 2009*; 34: 1929-1941 (48).

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

		Manchikanti et al (51)	Manchikanti et al (52)	Manchikanti et al (53)	Manchikanti et al (54)	Castagnera et al (55)	Stav et al (56)	Pasqualucci et al (57)
I.	**TRIAL DESIGN GUIDANCE AND REPORTING**							
1.	Consort or Spirit	3	3	3	3	1	1	1
II.	DESIGN FACTORS							
2.	Type and Design of Trial	2	2	2	2	2	2	2
3.	Setting/Physician	2	2	2	2	1	1	1
4.	Imaging	3	3	3	3	0	0	0
5.	Sample Size	3	3	2	2	0	0	0
6.	Statistical Methodology	1	1	1	1	1	1	1
III.	PATIENT FACTORS							
7.	Inclusiveness of Population	2	2	2	2	2	2	2
8.	Duration of Pain	2	2	2	2	2	2	1
9.	Previous Treatments	2	2	2	2	2	2	2
10.	Duration of Follow-up with Appropriate Interventions	3	3	2	2	1	1	1
IV.	OUTCOMES							
11.	Outcomes Assessment Criteria for Significant Improvement	4	4	4	4	2	2	2
12.	Analysis of all Randomized Participants in the Groups	2	2	2	2	2	2	2
13.	Description of Drop Out Rate	2	2	2	2	2	2	2
14.	Similarity of Groups at Baseline for Important Prognostic Indicators	0	1	1	1	1	1	1
15.	Role of Co-Interventions	1	1	1	1	1	1	1
V.	RANDOMIZATION							
16.	Method of Randomization	2	2	2	2	0	0	0
VI.	ALLOCATION CONCEALMENT							
17.	Concealed Treatment Allocation	2	2	2	2	0	0	0
VII.	BLINDING							
18.	Patient Blinding	1	1	1	1	0	0	0
19.	Care Provider Blinding	1	1	1	1	0	0	0
20.	Outcome Assessor Blinding	0	0	0	0	0	0	0
VIII.	CONFLICTS OF INTEREST							
21.	Funding and Sponsorship	2	2	2	2	2	2	2
22.	Conflicts of Interest	3	3	3	3	3	3	3
TOTAL MAXIMUM		43	44	42	42	25	25	24

Source: Manchikanti L, Hirsch JA, Cohen SP, Heavner JF, Falco FJE. Assessment of methodologic quality of randomized trials of interventional techniques: Development of interventional pain management specific instrument. Pain Physician 2014; 17: E263-E290 (49).

Table 4. *Study characteristics and results of cervical interlaminar randomized controlled trials.*

Study Study Characteristics	Participants/ Interventions	Outcome Measures	Pain Relief and Function				Results/Comment(s)
			3 mos.	6 mos.	12 mos.	2 years	
Manchikanti et al, 2013 (51) RA, AC, F Cervical disc herniation Quality Scores: Cochrane = 11/12 IPM-QRB = 43/48	Total = 120 Local anesthetic = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 83% vs LA with steroid 70% Successful: LA 91% vs. LA with steroid 84%	Overall: LA 82% vs LA with steroid 73% Successful: LA 91% vs. LA with steroid 86%	Overall: LA 72% vs LA with steroid 68% Successful: LA 77% vs. LA with steroid 82%	Overall: LA 72% vs LA with steroid 68% Successful: LA 77% vs. LA with steroid 80%	• Cervical interlaminar epidural injections were effective in 77% with local anesthetic or 80% with steroids in the successful groups after 2 years. • An active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.
Manchikanti et al, 2014 (52) RA, AC, F Cervical discogenic pain Quality Scores: Cochrane = 10/12 IPM-QRB = 44/48	Total = 120 Local anesthetic only = 60 Local anesthetic with steroids = 60 Local anesthetic or with Celestone Average number of injections = 5 to 6 for 2 years	Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 68% vs LA with steroid 77% Successful: LA 75% vs. LA with steroid 82%	Overall: LA 67% vs LA with steroid 73% Successful: LA 73% vs. LA with steroid 79%	Overall: LA 72% vs LA with steroid 68% Successful: LA 78% vs. LA with steroid 73%	Overall: LA 73% vs LA with steroid 70% Successful: LA 78% vs. LA with steroid 75%	• Cervical interlaminar epidural injections were effective in 78% with local anesthetic or 75% with steroids in the successful groups after 2 years. • An active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.
Manchikanti et al, 2012 (53) RA, AC, F Cervical spinal stenosis Quality Scores: Cochrane = 10/12 IPM-QRB = 42/48	Total = 60 Local anesthetic only = 30 Local anesthetic with steroids = 30 Local anesthetic or with Celestone Average number of injections = 3 to 4 for 2 years	Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 77% vs LA with steroid 87% Successful: LA 79% vs. LA with steroid 92%	Overall: LA 87% vs LA with steroid 80% Successful: LA 90% vs. LA with steroid 89%	Overall: LA 73% vs LA with steroid 70% Successful: LA 76% vs. LA with steroid 77%	NA	• Significant pain relief was seen in 87 % in both groups, while in Group I, 77 % and in Group II, 87% had functional status improvement. • An active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.
Manchikanti et al, 2012 (54) RA, AC, F Cervical post surgery syndrome Quality Scores: Cochrane = 10/12 IPM-QRB = 42/48	Total = 56 Local anesthetic only = 28 Local anesthetic with steroids = 28 Local anesthetic or with Celestone Average number of injections = 3 to 4 for one year	Significant improvement > 50% pain relief and > 50% functional status improvement	Overall: LA 68% vs LA with steroid 68% Successful: LA 83% vs. LA with steroid 72%	Overall: LA 64% vs LA with steroid 71% Successful: LA 78% vs. LA with steroid 80%	Overall: LA 71% vs LA with steroid 64% Successful: LA 87% vs. LA with steroid 72%	NA	• Cervical interlaminar epidural injections were effective in 87% with local anesthetic or 72% with steroids in the successful groups after 2 years. • An active-control trial conducted with fluoroscopy under appropriate circumstances in a private practice with contemporary interventional pain management techniques.

Table 4 (cont.). *Study characteristics and results of cervical interlaminar randomized controlled trials.*

Study Study Characteristics	Participants/ Interventions	Outcome Measures	Pain Relief and Function				Results/Comment(s)
			3 mos.	6 mos.	12 mos.	2 years	
Castagnera et al, 1994 (55) RA, AC, B Cervical disc herniation and radiculitis Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 24 Local anesthetic + steroid = 14 Local anesthetic + steroid + morphine = 10 Number of injections = 1	Pain relief, visual analog scale, work status	79.2%	79.2%	79.2%	NA	• 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 mos. • 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, 1993 (56) RA, AC, B Cervical disc herniation and radiculitis Quality Scores: Cochrane = 7/12 IPM-QRB = 25/48	Total = 42 Cervical epidural steroid/lidocaine injections = 25 Steroid/lidocaine injections into posterior neck muscles = 17 Number of injections = 1 to 3	Pain relief, change in range of motion, reduction of daily dose of analgesics, return to work	NA	NA	68% vs.11.8%	NA	• One year after the treatment, 68% of 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, 2007 (57) RA, AC, B Cervical disc herniation and radiculitis Quality Scores: Cochrane = 7/12 IPM-QRB = 24/48	40 of 160 Bupivacaine with methylprednisolone acetate 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.	Pain control of greater than 80%, pain-free hours of sleep	NA	Single vs. continuous 58.5%, 73.7% improvement	NA	NA	• 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 mos.

R = randomized; AC = active control; F = fluoroscopy; B = blind; LA = local anesthetic; IPM-QRB = Interventional Pain Management Techniques - Quality Appraisal of Reliability and Risk of Bias Assessment; NA = not applicable

tions in disc herniation or radiculitis (51,57-59). There was only one high quality randomized trial performed with an active-controlled design under fluoroscopic guidance (51). The remaining 3 studies of the epidural injections were performed blindly (57-59); one study described as a placebo-controlled design, administered steroids in the control group (58). Yet another study utilized morphine as an additive to the injected solution (57). Finally, the last study (59) compared continuous versus single epidural injections providing up to approximately 8 injections in the single group and assessed pain relief for only 6 month. The quality of these 3 studies performed without fluoroscopy was moderate.

Only one out of four randomized trial enrolled 120 participants with 60 subjects in each group, either with local anesthetic alone or local anesthetic plus 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 (56) where intramuscular steroid injections served as controls. However, this study enrolled only a small number 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 (51) 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, there was only one study for which the results were strong (51).

Axial or Discogenic Pain

There was only one study evaluating axial discogenic pain and the role of cervical interlaminar epidural injections in patients without disc herniation, radiculitis, or facet joint arthropathy (52). This study showed positive results. This was a large study performed in a contemporary interventional management practice setting utilizing an active-controlled 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.

Spinal Stenosis

There was only one randomized trial meeting the inclusion criteria in the evaluation of central spinal stenosis in the cervical spine (53). This study was of an active-controlled design and a preliminary report, but showed positive results.

Post Surgery 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-controlled design, but with preliminary results (54). The results were positive at 3, 6, and 12 months both for pain and functional status with or without steroids.

Meta-Analysis

No meta-analysis was performed, as none of the trials were homogenous for a specific condition. Only cervical disc herniation and radiculitis had a multiplicity of trials; although they were not homogenous. Among the 4 trials, one study compared local anesthetic with local anesthetic and steroids, a second study compared local anesthetic with steroids or steroid plus morphine, and the third trial compared local anesthetic with steroid or intramuscular steroids, and the fourth trial compared bupivacaine with methylprednisolone acetate in a short-term follow-up. In addition, follow-up was 2 years for one trial (51), one year for 2 of the trials (55,56), and only 6 months for one trial (57). Only one of the 4 trials (51) was conducted with fluoroscopy. The methodologic quality assessment also showed differences with one trial being high quality (51) and the remaining trials being moderate quality (55-57).

Analysis of Evidence

Since there was no meta-analysis feasible, qualitative evidence was synthesized based on the specific condition for which the cervical interlaminar epidural injections were provided. Table 4 shows the results of all the included randomized trials with the effectiveness of interlaminar epidural injections for 4 specific conditions, namely, disc herniation or radiculitis, axial or discogenic pain, central spinal stenosis, and post surgery syndrome.

Level of Evidence

Based on ASIPP's grading of evidence criteria, the evidence is considered at 5 levels (50).

Cervical Disc Herniation

For cervical disc herniation or radiculitis, based on one relevant high quality, large fluoroscopically direct-

ed active-controlled trial with local anesthetic with or without steroids (51), in conjunction with 3 moderate quality smaller randomized trials with positive results (55-57), the evidence is Level II supporting the benefit of cervical interlaminar epidural injections.

Axial or Discogenic Pain

For cervical axial or discogenic pain without facet joint pain, based on one relevant high-quality, large fluoroscopically directed active-controlled trial with local anesthetic with or without steroids (54), the evidence is Level II supporting the benefit of cervical interlaminar epidural injections.

Spinal Stenosis

For cervical central spinal stenosis or cervical radiculitis, based on one relevant high-quality, fluoroscopically directed active-controlled trial with local anesthetic with or without steroids (53), the evidence is Level II supporting the benefit of cervical interlaminar epidural injections.

Post Surgery Syndrome

For cervical post surgery syndrome based on one relevant high-quality, fluoroscopically directed active-controlled trial with local anesthetic with or without steroids (53), the evidence is Level II supporting the benefit of cervical interlaminar epidural injections.

Summary of Evidence

In summary, there is Level II evidence for cervical interlaminar epidural injections administered in managing disc herniation, central spinal stenosis, discogenic pain, and post surgery syndrome with local anesthetic with or without steroids based on high-quality RCTs.

Discussion

This systematic review on the effectiveness of cervical epidural injections in managing chronic neck pain with or without upper extremity pain assessed the efficacy of interlaminar epidural injections. There were, however, no randomized trials available for cervical transforaminal epidural injections. Based on relevant high-quality RCTs, the evidence shown here is Level II with at least one RCT for each pathologic condition, namely – cervical disc herniation and radiculitis, cervical central spinal stenosis, discogenic pain without facet joint pain or disc herniation, and cervical post surgery syndrome utilizing local anesthetic alone or with steroids.

Cervical disc herniation is readily diagnosed and one of the most common indications for surgical interventions in the spine. It is also believed that the course and prognosis of any spinal pain secondary to disc herniation and other causes are favorable; however, some patients continue to have persistent and disabling symptoms 2 years or longer and many undergo surgery. A multitude of surgical interventions in managing neck pain are becoming increasingly popular. The utilization of surgical interventions has increased 8-fold for anterior cervical discectomy and fusion from 1990 to 2004 with a 28-fold increase in those over 65 years of age (61). Overall there is concern about increasing surgical interventions and the success rate of these interventions, as they frequently result in post cervical surgery syndrome (62-70).

Similarly, assessments in Medicare populations (24-27) showed an increase of 142% from 2000 to 2011 per 100,000 Medicare beneficiaries of cervical and thoracic transforaminal epidural injections and 123% of cervical and thoracic interlaminar epidural injections (24). However, these increases are significantly less than other cervical and thoracic facet joint interventions, which showed respective increases of 359% for cervical and thoracic facet joint nerve blocks and 836% for cervical and thoracic neurolytic procedures (27). Overall, the contribution of thoracic spine interventions is considered minor compared to cervical spine ailments.

The results of this systematic review are similar to some previous reviews (19,20); they do not, however, correlate with other reviews that have not been performed appropriately due to an inadequate literature search. Furthermore, the results from lumbar epidural injections have also been reciprocated to the cervical spine. While the results may be similar in the entire spine, whether it is cervical, lumbar or thoracic, the evidence in the lumbar spine has been inappropriately synthesized. Of importance, the systematic review by Pinto et al (71) which showed the efficacy of epidural injections for short-term relief without lack of efficacy for long-term. The criteria for long term is arbitrary, most studies use 6 months and greater as long term. Further it is unrealistic to expect one or two ESI to provide long term relief of 12 months or longer in spinal stenosis and compare these outcomes with patients who are on long term analgesic therapy or those who undergo surgery. In contrast, Manchikanti et al (72-74) and others (6,75-78) have shown contradictory results showing the efficacy of epidural injections with caudal, interlaminar, and transforaminal approaches for both

the short term and long term when the analysis was performed appropriately. Pinto et al's (71) results have been criticized for multiple deficiencies (74,77,78). Pinto et al was criticized for utilizing methodological quality assessment criteria developed for physiotherapy, that the instrument was not validated for interventional techniques (74,79) and which differed substantially from criteria developed by the Cochrane review group (48). In contrast, in this systematic review we utilized strict methodological and bias assessment review criteria utilizing the well-established Cochrane review criteria instrument (48), as well as the recently developed IPM-QRB instrument (49), which incorporates all the ingredients necessary in the assessment of interventional techniques. In fact, the deficiencies of Cochrane review criteria have been addressed by others (78). In addition, Pinto et al (71) also included a multitude of heterogeneous studies that were labeled as homogeneous and conducted meta-analysis leading to inappropriate conclusions (74). The authors, in fact, have indicated erroneously that the studies were homogeneous based on the fact that reviewers decided that local anesthetic injection was a placebo (74). Such a methodology invalidates the entire concept of meta-analysis of homogenous studies. Pinto et al (71), similar to others (80-84), have utilized methodologies without attention to any clinical aspects. Pinto et al (71) also failed to consider the varying effects of placebo and nocebo, impure placebo, and the effects of injecting inactive solutions into active structures, concluding that injection of active solutions into active structures was placebo when it did not meet their criteria (6,85-87). In addition, multiple randomized trials, specifically of epidural injections utilizing only local anesthetic (51-54,88-95), have shown significant clinical effects. These effects were equal in the majority of the trials with the exception of a slight superiority in disc herniation confirmed by experimental studies (96,97) and a systematic review (78).

The underlying mechanism of action of epidurally administered steroids, local anesthetic the risks of local anesthetic have not been well understood (98-107). Steroids and local anesthetics have been described to exert their mechanism of action by a neural blockade that alters nociceptive input, the reflex mechanism of afferent fibers, self-sustaining activity of the neurons, and the pattern of central neuronal activities (6). In addition, corticosteroids have been shown to reduce inflammation by inhibiting either the synthesis or release of a number of proinflammatory mediators and by causing a reversible local anesthetic effect. The emerging evidence also shows the long-lasting effect of local anesthetics. It has been postulated that local anesthetics provide relief by multiple mechanisms that include the suppression of nociceptive discharge, the blockade of sympathetic reflex arc, the blockade of axonal transport, the blockade of sensitization, and anti-inflammatory effects (6). Clinical as well as experimental evidence shows a lack of significant difference between local anesthetic alone or with steroids indicating that corticosteroids may be unnecessary for spinal injections. A common problem encountered with any epidural injection, however, is inaccurate needle placement, as this leads to inaccurate placement of the injectate (19,20). Consequently, proponents for fluoroscopic guidance in epidural injections advocate utilizing this technique in order to assure that medications reach the appropriate desired intervertebral space (108-111). Furthermore, target specificity of epidural injections has also been questioned in the utilization of interlaminar cervical epidural injections (108-111).

Multiple authors have assessed prognostic factors for cervical epidural injections (112-117). In a retrospective evaluation (112), the influence of chronic opioid use is shown as a negative predictive factor for response to cervical epidural steroid injections. This concept has been addressed in multiple publications for surgical interventions. In fact, studies have shown that opioid withdrawal is a difficult task (118-121). Another assessment (114) showed that patients who required narcotics for their symptom management prior to the procedure showed poor pain relief. Radiographic assessment as a prognostic factor was evaluated in 2 assessments (113,122). In one manuscript (113) it was shown that magnetic resonance imaging (MRI) predicted therapeutic response to epidural 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. In contrast, others (115,116) have shown better improvement with disc herniation than spinal stenosis which is also reflected in the findings of lumbar epidural injections.

It is crucial that safety be considered in the utilization of epidural injections (19). Multiple risks include bleeding, non-fluoroscopic performance of the procedure, heavily sedated patients or those under general anesthesia, and performing the procedure above C5-C6 level (19). Serious complications can occur including spinal cord trauma or nerve trauma, infection, and epidural hematoma, even though intravascular penetration,

subarachnoid puncture, and injection of particulate steroids into the radicular artery are major complications specifically with cervical transforaminal.

Multiple technological modifications have been described to improve the safety and efficacy of transforaminal epidural injections (122-125).

There is a wide array of literature to improve the safety of cervical transforaminal epidural injections with a posterior approach, extraforaminal technique, utilizing special needles and catheters, etc. The detailed description of these aspects is beyond this manuscript (19).

The limitations of this systematic review include the paucity of high-quality literature for each modality, with only a total of 7 RCTs available, 4 of them assessing disc herniation, and one randomized high-quality trial assessing spinal stenosis and discogenic pain and post surgery syndrome. In addition, among the 4 trials available assessing disc herniation, there was only one high-quality trial. Consequently, without homogeneity among the randomized trials, we were unable to perform meta-analysis. In addition, all evidence was obtained from active-controlled trials, specifically for long-term improvement. Active-controlled trials compare 2 different procedures or drugs, thus, some may consider this as a weakness. One trial, described as placebo controlled, used intramuscular steroids, which also is an active-controlled trial. The majority of analytical flaws in evidence synthesis are based on methodologists repeatedly considering one of the drugs as placebo and comparing both drugs or both groups rather than baseline to follow-up periods, which is the only solution in active-controlled trials. Thus, the strengths of active-controlled trials include comparative evaluation, which has become pivotal in modern spine research given the difficulty associated with the design of appropriate placebo-controlled trials. However, there have been descriptions of appropriate placebo design, even in interventional techniques, in recent years with an inactive substance injected into an inactive structure. Thus, even though we considered active-controlled trials as a limitation, there are also multiple strengths to the use of active-controlled trials in deriving the evidence of efficacy. Furthermore, the strength of evidence we provided is qualitative evidence rather than quantitative evidence. We believe that this is appropriate since it is essential to assess the evidence appropriately rather than reach inappropriate conclusions with improper assessment.

The evidence seems to appear somewhat stronger for disc herniation with a multiplicity of studies in support and an absence of any negative studies to contradict these findings, even though only one was of high quality for spinal stenosis, discogenic pain, and post surgery syndrome. There was only one trial in each category that was of high quality. Both long-term studies with a large number of patients assessing disc herniation and discogenic pain were of active control nature.

Conclusion

This systematic review, with a proper assessment of methodological quality and risk of bias, shows Level II evidence, which supports the benefit of cervical interlaminar epidural injections based on at least one high-quality, relevant RCT for each etiology studied: disc herniation, discogenic pain without facet joint pain or disc herniation, central spinal stenosis, and post surgery syndrome.

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Conflict of Interest

Dr. Falco is a consultant for St. Jude Medical Inc. and Joimax Inc. Dr Sehgal is a consultant for Pfizer Inc, Mallinckrodt Inc and Pacira Inc.

Appendix 1. *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

Appendix 1. ***Randomized controlled trials quality rating system***.

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 from: Furlan AD, Pennick V, Bombardier C, van Tulder M; Editorial Board, Cochrane Back Review Group. 2009 updated method guidelines for systematic reviews in the Cochrane Back Review Group. *Spine (Phila Pa 1976)* 2009; 34:1929-1941 (48).

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

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

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

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

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

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

Source: Manchikanti L, Hirsch JA, Cohen SP, Heavner JF, Falco, FJE. Assessment of methodologic quality of randomized trials of interventional techniques: Development of an interventional pain management specific instrument. *Pain Physician* 2014; 17: E263-E290 (49).

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