Systematic Review

Transforaminal Versus Interlaminar Approaches to Epidural Steroid Injections: A Systematic Review of Comparative Studies for Lumbosacral Radicular Pain

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Background: The superiority of transforaminal epidural steroid injections (TFESI) vs. interlaminar epidural steroid injections (ILESI) for treating unilateral lumbosacral radicular pain (LSRP) is unproven.

Objective: To assess studies comparing TFESI to ILESI for unilateral LSRP for pain relief and functional improvement.

Study Design: Systematic review of comparative studies.

Methods: A systematic literature search was conducted using the Cochrane Central Register of Controlled Trials, PubMed, and Scopus databases for trials reported in English. Studies meeting the Cochrane Review criteria for randomized trials and the AHCQ criteria for observational studies were included. Evidence was graded using the USPSTF classification.

Results: Five (prospective) and 3 (retrospective) studies were included assessing 506 patients. Statistical analysis was calculated only utilizing the 5 prospective studies and consisted of 249 patients with an average of 3.2 months follow-up. In the short-term (2 weeks), there was a 15% difference favoring TFESI vs. ILESI for pain relief. There was no efficacy difference at one or 6 months. Combined pain improvements in all 5 prospective studies revealed < 20% difference between TFESI and ILESI (54.1% vs. 42.7%). There was slightly better functional improvement in ILESI groups (56.4%) vs. TFESI groups (49.4%) at 2 weeks. Combined data showed slight differences (TFESI 40.1% and ILESI 44.8%).

Limitations: The limitations of this systematic review include the relative paucity of comparative studies.

Conclusions: The findings show that both TFESI and ILESI are effective in reducing pain and improving functional scores in unilateral LSRP. In the treatment of pain, TFESI demonstrated non-clinically significant superiority to ILESI only at the 2-week follow-up. Based on 2 studies, ILESI demonstrated non-clinically significant superiority to TFESI in functional improvement.

Key words: Radiculopathy, epidural steroids, transforaminal, interlaminar, systematic review

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Transforaminal epidural steroid injections (TFESI) and interlaminar epidural steroid injections (ILESI) are commonly performed procedures for the management of unilateral lumbosacral radicular pain (LSRP). However controversy exists about the superior efficacy of one of these 2 interventional approaches respective to the other. Unilateral LSRP is thought to originate from inflammation in the proximity of a damaged intervertebral disc or a narrowed neural foramen that irritates an exiting spinal nerve root (1-4). Thus corticosteroids are commonly used to reduce inflammation in the epidural space (5-9). The purported advantage of TFESI over ILESI is attributed to enhanced deposition of medication in closest proximity to the pain generators found in the ventral epidural space (10), and hence reaching the targeted pain generators with a smaller dose of medication. Some evidence suggests that TFESI allow for greater ventral epidural spread of corticosteroid (11), and ventral epidural spread of corticosteroid has been associated with superior pain and functional outcome improvements (11). Data from multiple studies and systematic reviews of the published data support the utility of TFESI, and have shown that lumbar TFESI are effective for reducing pain, improving functionality, preventing spine surgery, and for treating radiculopathic pain (12-15). As a reflection of this perceived enhanced efficacy, there has been an exponential growth in the utilization of TFESI according to the Centers for Medicare and Medicaid Services (CMS) studies on utilization (15-17). Analysis of CMS data demonstrated that during the period from 2000 to 2011, utilization of lumbosacral TFESI grew at an annual rate of 20.4%, whereas lumbosacral interlaminar and caudal injections grew at a comparatively modest annual rate of 2% (16).

Despite the touted advantages for TFESI, the technique has been noted to carry certain unique risks. TFESI are more often implicated in severe, permanent complications compared to ILESI, including intravascular injection in up to 23% of lumbar epidural injection cases (18), which can lead to spinal cord infarction and paralysis (19-21). Intravascular injection with TFESI can occur even with the use of digital subtraction angiography or following a negative lidocaine anesthetic test dose (19). TFESI, compared to ILESI, are associated with a 12-fold increased risk of intradiscal injection (22,23), which can potentially weaken the disc or lead to discitis (24). Additionally, TFESI do not decrease the risk of known complications of ILESI, such as dural and subdural punctures (25), hematoma formation (26-30), and cauda equina syndrome (31). With regards to global outcome in an individual with lumbosacral radicular pain, the increased risk of complications associated with TFESI must be weighed against possibility for superior pain relief and functional outcomes that reduce the rate of spinal surgery (32), which is itself associated with significant vascular, neurologic, urologic, and infectious complications (33-35). However it remains unclear if TFESI result in clinically or statistically significant improvement in pain and functional outcomes compared to ILESI.

The existing data suggests long-term efficacy benefits are greater for TFESI compared to ILESI (12-14,32,36). However, conflicting data also exist for equivalent benefits between the 2 techniques as well (37-39). Many authors have performed systematic reviews on the efficacy of epidural steroid injections leading to a range of conclusions. However, there are only few well-designed, prospective, randomized, double-blind, controlled studies. Importantly, several studies have directly compared these 2 approaches with conflicting results. Our goal was to systematically review, grade the evidence, and perform a meta-analysis of the existing head-to-head comparative studies. In this review, we identified the available published data comparing the short- and long-term efficacy of TFESI and ILESI for improving pain and functionality in individuals with unilateral lumbosacral radicular pain.

Methods

Study Design

The standards set by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were used to construct this systematic review. The 27-item checklist and 4-phase flow diagram were accessed from the PRISMA website on July 29, 2013.

Eligibility Criteria

For inclusion in the present systematic review, papers had to report the results of clinical studies evaluating transforaminal versus interlaminar epidural steroid injections. More specifically, articles had to meet the following eligibility criteria: (1) human adult men and women (> 18 years) suffering from unilateral lumbosacral radicular pain were evaluated; (2) patients' symptoms were secondary to intervertebral disc herniations/degeneration; (3) patients were followed-up a minimum of 2 weeks; (4) papers were published in English prior to August 2013.

Randomized controlled trials were identified as the primary studies for analysis. To be included, for statistical analysis, patients must have been randomized to TFESI or ILESI.

Non-randomized studies were also identified for secondary review if a small number of RCTs were found.

Studies were excluded from analysis if they had poorly described needle placement methodology, did not use fluoroscopic guidance for needle placement, did not report standardized pain scores at defined follow-up intervals, or did not provide statistical analyses of their results. Review articles, letters to the editor, and studies that did not directly compare TFESI versus ILESI as epidural steroid injections were excluded from consideration.

Literature Search

We conducted a comprehensive literature search of Medline (PubMed)®, Cochrane Central Register of Controlled Trials (CENTRAL), and Scopus databases for relevant English language publications from 1966 through August 2013 in order to identify studies that specifically compared lumbar transforaminal to interlaminar epidural steroid injections in the treatment of unilateral lumbosacral radicular pain. Search terms included, "Transforaminal Epidural Steroid Injection"; "Interlaminar Epidural Steroid Injection"; "Efficacy of Transforaminal Epidural Steroid Injection"; "Efficacy of Interlaminar Epidural Steroid Injection"; "Transforaminal versus Interlaminar Epidural Steroid Injection"; "Efficacy of Transforaminal versus Interlaminar Epidural Steroid Injection"; "Selective Nerve Root Block versus Interlaminar Epidural Steroid Injection"; "Transforaminal versus Interspinous Injections"; and "Nerve Root Block versus Interspinous Injection."

References from each article directly comparing the 2 approaches, in addition to review articles discussing efficacy of the 2 approaches, were cross-referenced in order to identify additional relevant studies. The literature search methodology was developed by the first 3 authors (GCC, ZM, SK), and conducted by 2 independent reviewers (GCC and SK). Any differences in selected papers for inclusion and exclusion were resolved by consensus.

Outcome Parameters

The primary outcome measure was efficacy determined as "degree of pain relief" (visual or verbal analog pain score; numeric pain rating scale). The secondary outcome measure was functional improvement (Oswestry Disability Index, Depression Numeric Rating Scale, city block walking tolerance, Global Perceived Effect, and Oswestry Low Back pain scale-EIFEL). We considered a difference in pain scores of at least 30% as being clinically significant. In order to determine the duration of effect measured, we looked for follow-ups at regular intervals, including at 2 weeks, 4 weeks, and 6 months with 4 weeks being considered a short-term effect; and 6 months being considered an intermediate-term effect. We accepted this duration upon recommendations suggested in the above-referenced Cochrane review (40).

The Cochrane Review criteria (41) for randomized trials and the Agency for Health Care Quality (AHCQ) criteria (42) for observational studies were applied to ensure that the studies considered used proper methodology. Studies that scored higher than 50 out of 100 using these measures were included (Tables 1 and 2). Each study was scored independently by 2 of the authors (ZM, SKC), and a third author (GCC) independently reviewed studies that were scored differently by the first 2 authors. This weighted scoring system has been used in multiple systematic reviews of interventional treatment for back pain (12,14,41,43-58).

Risk of Bias

The Cochrane Risk of Bias Tool was utilized to systematically assess for bias in identified prospective studies. The support judgments for each manuscript can be found in the (Table 3). The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the identified non-randomized trials (wells). The lead (GCC) and secondary authors (NNK) assessed each study for bias to ascertain a consensus grading (Table 4).

Grading Quality of Evidence

The United States Preventive Services Task Force (USPSTF) level of evidence classification (59) (Table 5) was used to grade the level of evidence reported in the literature describing the comparison of TFESI vs. ILESI for the treatment of lumbosacral radicular pain.

Statistical Analysis

Statistical analysis was performed using SPSS (IBM SPSS Statistics 20, Chicago, IL) and MedCalc 12.7.0 (Ostend, Belgium) software. Differences in age, pain, and functional improvement between TFESI and ILESI were analyzed using independent samples t-test. Differences in gender, level of injection, or type of corticosteroids between the 2 groups were analyzed by $\chi 2$ test. For-

Table 1. *Methodological assessment of randomized controlled trials comparing the efficacy of transforaminal to interlaminar epidural steroid injections.*

	Weight (points)	Gharibo et al (68)	Candido et al (37)	Rados et al (67)	Ackerman and Ahmad (11)	Kolsi et al (69)
Study Population	**35**					
Homogeneity	**2**	2	2	2	2	2
Comparability of relevant baseline characteristics	**5**	3	3	3	4	5
Randomization procedure adequate	**4**	4	4	4	4	2
Drop-outs described for each study group separately	**3**	3	3	3	3	3
≤ 20% loss for follow-up	**2**	2	2	2	2	2
≤ 10% loss for follow-up	**2**	2	2	2	2	2
> 50 subject in the smallest group	**8**	0	0	0	0	0
> 100 subjects in the smallest group	**9**	0	0	0	0	0
Interventions	**25**					
Interventions included in protocol and described	**10**	10	10	10	10	10
Pragmatic study	**5**	5	5	5	5	5
Co-interventions avoided or similar	**5**	5	5	5	5	5
Placebo-controlled	**5**	0	0	0	0	0
Effect	**30**					
Patients blinded	**5**	5	5	5	5	5
Outcome measures relevant	**10**	6	2	6	6	6
Blinded outcome assessments	**10**	10	0	0	10	10
Follow-up period adequate	**5**	3	5	5	5	3
Data Presentation and Analysis	**10**					
Intention-to-treat analysis	**5**	0	0	0	5	0
Frequencies of most important outcomes presented for each treatment group	**5**	5	5	5	5	5
Total Score:	**100**	65	53	57	63	65

* Above Cochrane Review criteria for randomized trials adapted from ref. 41

est plots and I^2 calculation were performed using the MedCalc 12.7.0 software.

Results

Literature Search

In our exhaustive literature search, 1,007 references were identified using the key words. Subtracting 625 duplicate items, 372 articles were screened for review. We identified 12 studies that specifically compared transforaminal to interlaminar approaches of epidural steroid injection for the treatment of unilateral LSRP which were subsequently assessed for eligibility (Fig. 1).

Kraemer et al (60) compared non-conventional interlaminar epidural steroid injections with epidural perineural injections, wherein a needle was passed towards the medial neuroforamen from the interlaminar space. This study was excluded from analysis due to a lack of consistent use of fluoroscopic guidance, and the unique procedural approach employed. The largest study comparing TFESI to ILESI was from Lee et al (38), but it was excluded from analysis as patients with lumbosacral radicular symptoms were paradoxically excluded from their study. The use of fluoroscopy is acknowledged as being superior to blind epidural steroid injection due to the high false positive rate with the loss of resistance (LOR) technique without fluoroscopic

Table 2. *Methodological Assessment of retrospective studies comparing the efficacy of transforaminal to interlaminar epidural steroid injections.*

Criterion	Smith et al (72)	Lee et al (73)	Schaufele et al (70)
1. Study Question			
Clearly focused and appropriate question	2	2	2
2. Study Population			
Description of study population	2	2	0
Sample size justification	0	0	0
3. Comparability of Subjects			
Specific Inclusion/Exclusion Criteria for all groups	5	5	5
Criteria applied equally to all groups	3	3	3
Comparability of groups at baseline with regard to disease status and prognostic factors	3	2	2
Study Groups comparable to non-participants with regard to confounding factors	3	3	0
Use of concurrent controls	0	0	0
Comparability of follow-up of each group at assessment	3	2	3
4. Exposure or Intervention			
Clear definition of exposure	5	5	5
Measurement method standard, valid and reliable	3	3	3
Exposure measured equally in all study groups	3	3	3
5. Outcome Measures			
Primary/secondary outcomes clearly defined	5	5	5
Outcomes assessed blind to exposure or intervention	5	3	0
Method of outcome assessment standard, valid and reliable	5	5	5
Length of follow-up adequate for question	5	5	0
6. Statistical Analysis			
Statistical tests appropriate	5	5	5
Multiple comparisons taken into consideration	1	2	3
Modeling and multivariate techniques appropriate	2	2	2
Power calculation provided	0	0	0
Assessment of confounding	0	0	0
Dose-response assessment if appropriate	2	2	0
7. Results			
Measure of effect for outcomes and appropriate measure of precision	3	3	5
Adequacy of follow-up for each study group	3	3	3
8. Discussion			
Conclusions supported by results with possible biases and limitations taken into consideration	4	5	5
9. Funding or Sponsorship			
Type and sources of support for study	5	3	5
TOTAL SCORE	**78**	**73**	**64**

*Above Agency for Health Care Quality criteria for observational studies adapted from West S et al (42).

Table 3. *Risk for bias in prospective studies.*

	Sequence generation	Allocation concealment	Blinding	Incomplete outcomes Data	Selective outcomes reporting	Other sources of bias	Confounding
Gharibo et al (68)	Low Risk "Participants were randomly assigned to one of 2 groups using a computer-generated randomization table."	Low risk "Allocation to injection type was randomly computer generated."	Low risk The interventionalist was blind to participant data.	Low risk	Low risk	Low risk No conflicts reported.	Low risk
Candido et al (37)	Low Risk "Patients were randomly assigned to one of two groups using a computer-generated randomization table."	Unclear risk	Unclear risk	Low risk All expected outcomes reported.	Low risk All expected outcomes reported.	Low risk	Low risk
Rados et al (67)	Low risk "Computer generated randomization."	Unclear risk	High risk "The participants in the study were blinded throughout the study……..while the authors were not blinded."	Low risk All expected outcomes reported.	Low risk All expected outcomes reported.	Low risk	Low risk
Ackerman and Ahmad (11)	Low risk "computer generated randomization."	Unclear risk	High risk	Low risk All expected outcomes reported.	Low risk All expected outcomes reported.	Low risk	Low risk
Kolsi et al (69)	High risk "Immediately before the injection the patients were randomized by the physician who was to perform the injection. This physician did not see the participants at any other time during the study."	High risk	Low risk	Low risk All expected outcomes reported.	Low risk All expected outcomes reported.	Low risk	Low risk

Table 4. *Newcastle-Ottowa Scale.*

	Selection	Comparability	Outcome
Lee et al (73)	XXXX	X	XX
Schaufele et al (70)	XXXX	X	XX
Smith et al (72)	XXXX	X	XX

Table 5. *United States Preventative Services Task Force Quality of Evidence Classification .*

I	At least 1 randomized controlled trial
II-1	Prospective, placebo-controlled trials that are not-randomized
II-2	Controlled retrospective studies
II-3	Uncontrolled retrospective studies
III	Descriptive studies

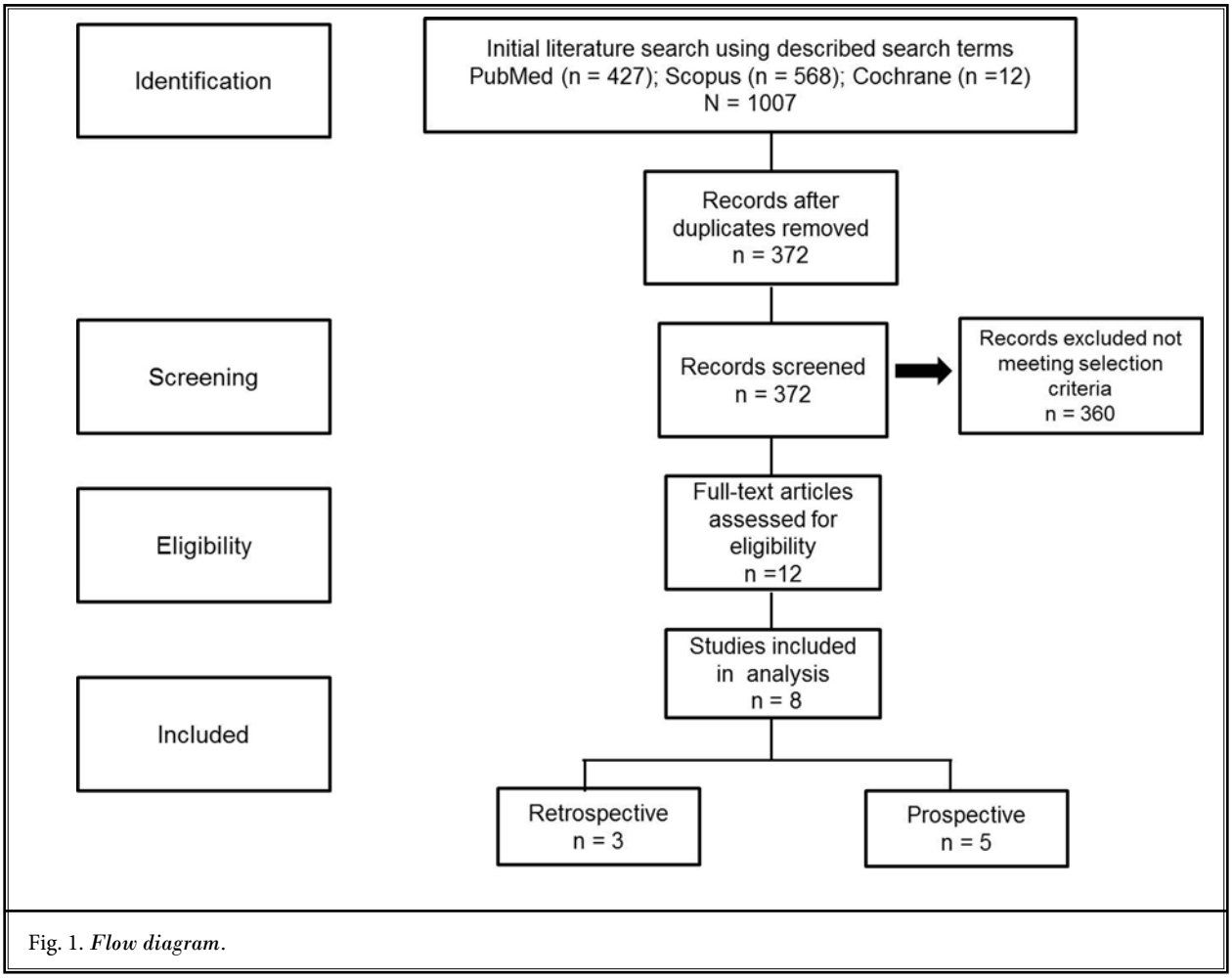

Fig. 1. *Flow diagram*.

confirmation (61-63). Thus, 2 studies (64,65) were excluded because of the lack of fluoroscopic guidance in performing injections. Direct comparative studies that did not meet inclusion/exclusion criteria are listed in the Table 6. Thus 8 studies were considered for inclusion. Although some studies included caudal epidural steroid injection as part of their research protocol (11), only data on TFESI or ILESI were included for analysis.

Screening for Methodological Quality of Studies

Five out of 8 studies included were prospective and 3 were retrospective. The 5 prospective studies identified met the Cochrane Review criteria for randomized trials (41) (Table 2) and 3 studies met the Agency for Health Care Quality (AHCQ) criteria for observational studies (42). All studies surpassed 50 out of 100 on a modified and weighted Cochrane methodologic quality assessment criteria (66) (Table 1). A summary of study criteria for included prospective studies is listed in the Table 7. Retrospective studies were included in the review due to the paucity of prospective data (Table 2), but are not included in analysis of pain or functional improvement.

Demographics Inclusion/Exclusion Criteria

The total number of patients in all 8 studies was 506, comprising 249 patients in the prospective studies, and 257 patients in the retrospective trials. In the 5 prospective trials, patients were followed up an average of 3.2 months, (range: 10 – 16 days following injection (11) for up to 6 months) (37,64,67).

Statistical analysis was calculated utilizing the 5 prospective studies. There was a slight difference in

Table 6. *Direct comparative studies that did not meet inclusion/exclusion criteria.*

Author	Study Type	Type of pain	TFESI	ILESI	Fluoroscopy	Reason for Exclusion
Kraemer et al (60)	Prospective randomized	Radicular pain	Non-conventional	Midline	Inconsistent use	Inconsistent fluoroscopy
Lee et al (73)	Prospective randomized	Axial back pain without radiation	Bilateral TFESI	Midline or posterior lateral	Yes	Axial back pain not radicular
Thomas et al (64)	Prospective Randomized	Radicular pain	Unilateral TFESI "safe triangle"	Midline	ILESI performed without contrast	No contrast used for fluoroscopy
Manchikanti et al (65)	Retrospective	Low back and radicular pain	Unilateral TFESI	Loss of resistance	ILESI without fluoroscopy	No fluoroscopy

Table 7. *Summary of Study criteria - prospective studies.*

Author	Symptom	Cause of Pain	Baseline Pain Score	Duration of Symptoms
Gharibo et al (68)	unilateral lumbosacral radicular pain	Intervertebral herniated disc	ILESI: 7.0 ± 1.9; TFESI: 6.4 ± 2.1	>1 Month < 1 Year
Candido et al (37)	unilateral lumbosacral radicular pain	Intervertebral herniated disc	ILESI: 6.78 ± 2.44; TFESI: 6.32 ± 2.23	>15 days
Rados et al (67)	unilateral lumbosacral radicular pain	Intervertebral herniated disc excluding SS	ILESI: 7.36 ± 1.6; TFESI: 6.72 ± 1.8	> 6 weeks < 1 year
Ackerman and Ahmad (11)	unilateral lumbosacral radicular pain	Intervertebral herniated disc	ILESI: 8.8 ± 0.8 TFESI: 8.6 ± 0.9	ILESI 33 ± 7 days, TFESI 35 ± 5 days
Kolsi et al (69)	unilateral lumbosacral radicular pain	Intervertebral herniated disc	ILESI: 6.3 ± 0.4 TFESI: 7.0 ± 0.4	>15 days

gender distribution (62.5% men received TFESI; 54.4% men received ILESI; $P < 0.001$). The average age of patients receiving TFESI was 45.03 ± 6.58 years vs. 48.77 ± 10.08 years in the ILESI group ($P < 0.001$). A majority of patients received injections at the L5-S1 level (64.3%), vs. at the L4-L5 level (33.9%) while only 1.8% were injected at either the L2-L3 or L3-L4 levels ($P = 0.718$).

Type of Corticosteroids

A majority of patients received either triamcinolone (n = 277; 55%) or methylprednisolone acetate (n = 199; 39%). The remainder received cortivazol (n = 30; 6%), a synthetic agonist ligand that has a high affinity for the glucocorticoid receptor. There was an equal distribution of corticosteroids between TFESI and ILESI in all studies. The medication preparations for each study are summarized in Table 8.

Procedure Techniques

A variety of technical differences were noted between the studies in this review. Methodological differences in needle selection, use of fluoroscopy, and final needle tip position are summarized in Table 9.

Outcomes and Clinical Significance

Individual study outcomes and the presence of clinical significance are summarized below and in Table 8.

Pain Improvement as Efficacy

All 5 prospective studies provided data regarding improvement in pain scores. Combined pain improvements looking at the end-time points in all 5 studies revealed a less than 20% difference between TFESI and ILESI (54.1% vs. 42.7%). Meta-analysis was performed, even though the heterogeneity was high (I^2 up to 87%), and showed slightly better pain improvement after TFESI injections only after 2 weeks of follow-up (Fig. 2b), with no difference noted after one and 6 month follow-ups (Fig. 2c, d).

Gharibo et al (68) followed patients for approximately 2 weeks (10 – 16 days). While Ackerman and Ahmad (11) followed patients for 24 weeks in their prospective study, and documented pain score improvements only after the first 2 weeks. Candido et al (37) also reported pain scores at 2 weeks and for up to six months. All 3 studies demonstrated an approximately 15% difference favoring efficacy from TFESI compared

Table 8. *Summary of head-to-head studies comparing TFESI vs. ILESI.*

Author	Study Type	Cause of Lumbar Radicular Pain	TFESI	ILESI	Duration of Follow-Up	Pain Improvement TFESI vs. ILESI	Functional Improvement TFESI vs. ILESI
Gharibo et al (68)	Prospective Randomized Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 20 40 mg triamcinolone + 1 mL 0.25% bupivacaine At 2 levels Vol: 4 mL	n = 18 80 mg triamcinolone + 2 mL 0.25% bupivacaine Vol: 4mL	10-16 days	73.4% vs. 44.3%	43.6% vs. 49.3%
Candido et al (37)	Prospective Randomized Single-Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 28 80 mg MPA + 1 mL 1% lidocaine + 1 mL NSS Vol: 4 mL	n = 29 80 mg MPA + 1 mL 1% lidocaine + 1 mL NSS Vol: 4 mL	1 month 6 months	16.5% vs. 23.1% 25.5% vs. 39.2%	N/A N/A
Rados et al (67)	Prospective Randomized (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 32 40 mg MPA + 3 mL 0.5% lidocaine Vol: 5 mL	n = 32 80 mg MPA + 8 mL 0.5% lidocaine Vol: 10 mL	24 weeks	45.6% vs. 43.5%	28.3% vs. 25%
Ackerman and Ahmad (11)	Prospective Randomized Blinded (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 30 40 mg triamcinolone + 4 mL NSS Vol: 5 mL	n = 30 40 mg triamcinolone + 4 mL NSS Vol: 5 mL	2 weeks 24 weeks	72.1% vs. 35.2% N/A	53.3% vs. 60.6% N/A
Kolsi et al (69)	Prospective Randomized Double-Blinded	Lumbar Disc Herniation and/or Spinal Stenosis	n = 17 3.75 mg Cotivazol Vol: 1.5 mL	n = 13 3.75 mg Cotivazol Vol: 1.5 mL	28 days	62.8% vs. 63.5%	34.8% vs. 50.9%
Smith et al (72)	Retrospective Case-control (Level II-3)	Spinal Stenosis	n = 19 80 mg MPA + 1-2 mL 2% lidocaine Vol: 3-4 mL	n = 19 80 mg MPA + 2 – 3 mL 1% lidocaine Vol: 4 – 5 mL	4- 6 weeks	30.5% vs. 39.5%	N/A
Lee et al (73)	Retrospective Case-control (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 115 40 mg triamcinolone + 2 or 8 mL 0.5% lidocaine Vol: 3 or 9 mL	n = 64 40 mg triamcinolone + 8 mL 0.5% lidocaine Vol: 9 mL	1 month 2 months	78.0% v. 64.5% 68.2% vs. 51.6%	N/A N/A
Schaufele et al (70)	Retrospective Case-control (Level 1)	Lumbar Disc Herniation and/or Spinal Stenosis	n = 20 80 mg MPA + 1-2 mL 2% lidocaine Vol: 3-4 mL	n = 20 80 mg MPA + 2 – 3 mL 1% lidocaine Vol: 4 – 5 mL	2-3 weeks	45.8% vs. 19.2%	N/A

Key: Vol = Total volume

with ILESI groups (54.7% vs. 39.2%). Gharibo et al (68) studied 38 patients, but did not provide long-term outcome follow-up (merely 10 – 16 days), and all injections were performed by a single practitioner. Patients from the TFESI group had statistically significantly better pain improvement, but all TFESI were performed using a 2-level, 2-needle technique (i.e., "double level TFESIs") with medication injected at adjacent contiguous neuroforamina.

Two prospective studies (37,69)) provided pain

Table 9. *Summary of techniques utilized.*

Author	TFESI			ILESI		
	Flouroscopy	**Needle Type**	**Needle Position**	**Fluoroscopy**	**Needle Type**	**NeedlePosition**
Gharibo et al (68)	Contrast dye	Two 22-gauge 3½-inch spinal needles	"safe triangle"	Contrast dye	18-gauge Tuohy	Interlaminar Loss of resistance to air
Candido et al (37)	Contrast dye	22-gauge 3½-inchWhitacre	Superior-posterioneuro-foramen	Contrast dye	20-gauge 3½-inch Tuohy	Parasagittal Interlaminar Loss of resistance to air
Rados et al (67)	Contrast dye	22-gauge needle	Not provided	Contrast dye	19-gauge Touhy	Interlaminar Loss of resistance to air with glass syringe
Ackerman and Ahmad (11)	Contrast dye	22-gauge Touhy	Superior-posteriorneuro-foramen	Contrast dye	22-gauge Touhy	Not provided
Kolsi et al (69)	Contrast dye	Not provided	Nerve root injection	Contrast dye	Not provided	Not provided
Smith et al (72)	Contrast dye	25- or 22-gauge 3½-inch or 5-inch spinal needle	Superior-anteriorneuro-foramen	Contrast dye	18-gauge 3½-inch or 5 inch Tuohy	Parasagittal Interlaminar Loss of resistance to air
Lee et al (73)	Contrast dye	22-gauge spinal needle	Superior-anteriorneuro-foramen	Contrast dye	18-gauge 3½-inchTuohy	Interlaminar Loss of resistance to air
Schaufele et al (70)	Contrast dye	25- or 22-gauge 3½-inch or 5-inch spinal needle	Superior-anteriorneuro-foramen	Contrast dye	18-gauge, 3½-inch or 5-inch Tuohy	Parasagittal Interlaminar Loss of resistance to air

score data at one month following injections. Both studies demonstrated virtually no efficacy differences between approaches (34.0% TFESI vs. 35.6% ILESI). Based on Cochrane review guidelines, this difference was not considered clinically significant. Kolsi et al (69) found no significant efficacy differences between TFESI and ILESI in the short- or long-term follow-ups. A limitation of this study was the small sample size (n = 40). Two prospective studies (37,67) followed patients for at least 6 months and provided data regarding pain improvement expressed as a numeric rating pain score. Both studies showed slightly better pain improvement after ILESI than TFESI injections (41.5% vs. 36.2% pain improvement). Candido et al (37) showed no difference in pain scores between TFESI and ILESI performed using a lateral parasagittal interlaminar approach, on short- (one month) or long-term (6 months) follow-ups. Rados et al (67) also showed no statistically significant difference between the 2 approaches. A major limitation of this study was the use of different protocols for injectate mixtures and volumes. Ackerman and Ahmad (11) showed better pain improvement at 24 weeks in a TFESI group. However, the pain improvement was graded as complete, partial, or no relief, and was not assessed using conventional numeric rating scale (NRS) scores. NRS scores were not used in the combined analysis for the 6-month follow up. They showed that out of 30 patients who had ILESI injections, 3 (10%) reported complete pain relief, 15 (50%) partial pain relief, and 12 (40%) demonstrated no relief. Of the 30 patients who had TFESI injections, 9 (30%) reported complete pain relief, 16 (53%) had partial pain relief, and 5 (17%) had no relief. However, different volumes and doses of medication were used in both approaches.

Functional Improvement

Four of 5 prospective studies included in our systematic review measured functional improvement as one of their study outcomes. Three studies (11,67,68) used the Oswestry Disability Index (ODI and one used the EIFEL score (69), which is the French version of the Roland-Morris Disability Questionnaire for low back pain. Meta-analysis was performed even though the heterogeneity was high (I^2 = 65.5%), showing better functional improvement after ILESI injections (Fig. 3a, b).

Two studies provided data for functional improvement at approximately 2 weeks (11,68) and showed a slightly better functional improvement in the ILESI

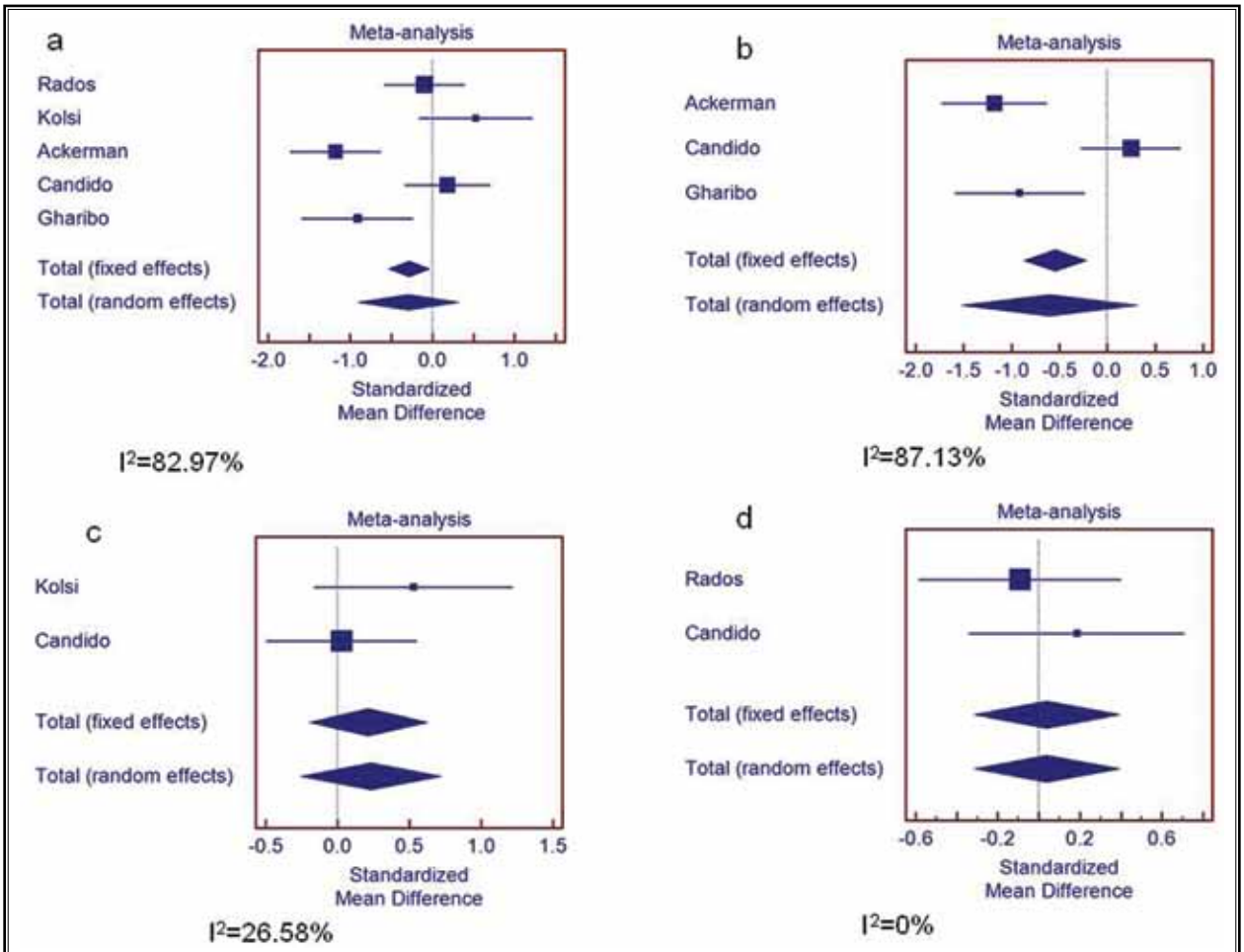

Fig. 2. *Meta-analysis of pain improvement after TFESI injections.*

group (56.4%) compared with the TFESI group (49.4%). One study (69) provided data for a one-month follow-up and found significantly better functional improvement in the ILESI than in TFESI group (50.9% vs. 34.8%). Also, one study (67) that followed patients for 6 months showed slightly better functional improvement in the TFESI group (28.3%) than in the ILESI group (25.0%). Combined data from all 4 studies showed only slight differences between these 2 approaches (TFESI 40.1% and ILESI 44.8%).

Other Outcomes

Candido et al (37) used the contrast spread pattern between TFESI and ILESI approaches as the primary outcome measure in their study, along with total fluoroscopy time and pain relief as secondary measures. An independent blinded radiologist graded the lateral projection fluoroscopic images from each patient. Patients in the parasagittal ILESI group demonstrated more consistent anterior epidural spread (29 of 29; 100%), compared to 21 of 28 (75%) patients in the TFESI group. Mean continuous fluoroscopy time was 28.96 seconds (95% CI, 23.9 – 34.1 seconds) in the parasagittal ILESI group and 46.25 seconds (95% CI, 36.27 – 56.23 seconds) in the TF group ($P = 0.003$) (37). Ackerman and Ahmad (11) also looked at the contrast spread and pain relief at 24 weeks, finding that patients wherein ventral epidural spread was documented had more complete pain relief, while patients with non-ventral spread had more incomplete pain relief regardless of which approach was used.

Level of Evidence

In the treatment of lumbosacral radicular pain due

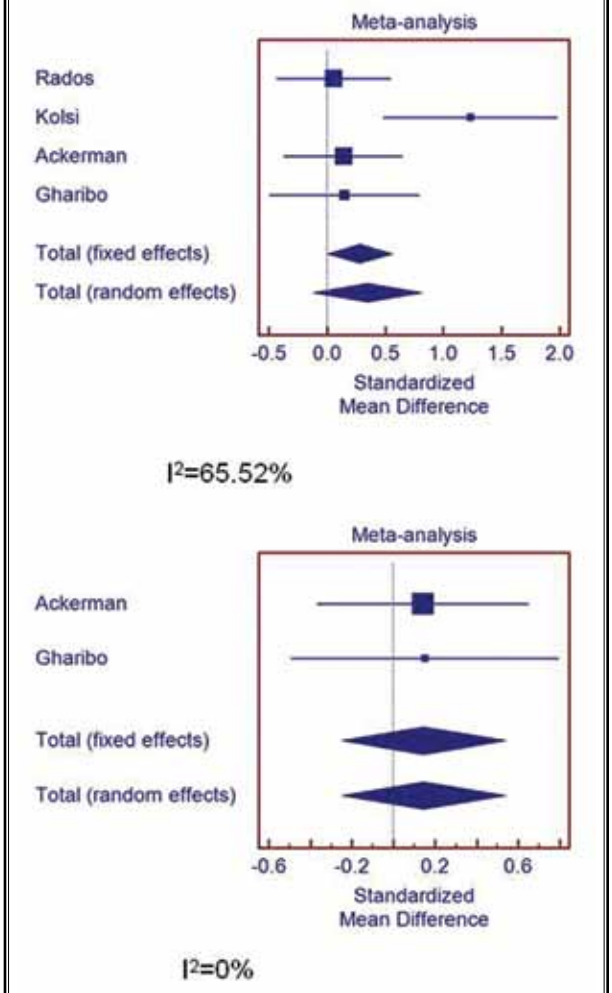

Fig. 3. Meta-analysis showing better functional improvement after ILESI injections.

to disc herniation, there is Level 1 evidence for significant improvement in pain scores with fluoroscopically guided TFESI compared to fluoroscopically guided ILESI in both the short-term: 2 RCTs (11,68), one retrospective study (RS) (70), and one long-term RCT (11). These findings are opposed by Level 1 evidence finding no difference between these groups in the short-term: 3 RCTs (37,67,69), and long-term: 3 RCTs from the same authors (31,67,69).

There is Level 1 evidence for no difference in improvement of function between fluoroscopically guided TFESI compared to fluoroscopically guided ILESI groups in both short-term: 3 RCTs (11,67,68), and long-term: 2 RCTs (11,67).

Discussion

The total number of patients identified in the 5 prospective studies that met criteria for this review was 249. There was a 15% difference favoring efficacy of TFESI compared with ILESI only in the short-term (2 weeks) follow-up period. Studies that followed patients from between one to 6 months, as well as combined pain improvements when looking at end points "time," identified no clinical or statistically significant differences in efficacy between TFESI and ILESI. Four prospective studies included in our systematic review that measured functional improvement and that followed patients from between 2 weeks to one month found better functional improvement in the ILESI groups. However, none of these differences were considered clinically significant, according to Cochrane review guidelines (40).

For the treatment of unilateral lumbosacral radicular pain due to intervertebral disc herniation, the head-to-head evidence is mixed as to whether TFESI is superior to ILESI for clinically significant improvements in pain and functional outcomes, versus whether the 2 techniques are equivalent. We could find no study demonstrating superior efficacy outcomes of ILESI compared to TFESI for either pain reduction or functional improvement.

Although not shown in any of the studies within this review, TFESI have been shown to provide pain relief lasting upwards of 12 months (71). It is a widely held belief that increased deposition of medication into the ventral epidural space will result in greater efficacy and subsequent reduction in pain scores. We found only one head-to-head study to support this conclusion (11). Although Ackerman and Ahmad (11) performed a randomized, blinded prospective trial, the study results have limited clinical utility due to multiple methodological limitations including: the specific inclusion of radicular pain in an S1 dermatomal distribution; the use of repeat injections 2 weeks apart, as part of a series of 3 injections; and documented pain score improvement only after the first 2 weeks, even though patients were followed for 24 weeks (11). The majority of studies included in our review used a midline approach to ILESI. Currently, only one prospective study (37) and 2 retrospective studies (70,72) have directly compared parasagittal (non-midline) ILESI to TFESI. Two studies found no difference for both short- and long-term pain outcomes between TFESI and parasagittal ILESI. Schaufele et al

(70) found no difference in pain scores post-injection between TFESI and ILESI. However, the authors claimed a statistically significant superiority of TFESI for pain relief during a follow-up at up to 12 months. This conclusion is limited by repeated and uncontrolled use of additional epidural steroid injections and surgical interventions at undefined intervals during that 12 month period. There is evidence that a parasagittal ILESI approach may provide comparable ventral flow of corticosteroids (37) as well as similar pain relief and functional changes when compared to TFESI. Indeed, although midline ILESI epidurography patterns may demonstrate ventral epidural spread of the contrast as low as 36% of the time (1), one study in our review found ventral spread with parasagittal ILESI in 100% of subjects (37). As highlighted in the results section, this study demonstrated no difference in pain or functional outcomes between TFESI and parasagittal ILESI at 2 weeks, one, 3, and 6 months (37). Given the rare but serious complications associated with TFESI, further head-to-head study of parasagittal ILESI compared to TFESI appears to be warranted.

Some practitioners have attempted to utilize the purported advantages of the TF approach, i.e. deposition of the medication into the ventral epidural space, by accessing the neuroforamen via the interlaminar window (as an "inside-out" type of approach) (73,74). These approaches are much less commonly performed than classical TFESI ("outside-in") and statistics for efficacy and complications are not available. There is no evidence that this type of approach decreases risks of morbidity or mortality associated with TFESI and further studies are necessary to delineate its role in the management of lumbosacral radicular pain.

The findings reported herein must take into account several important considerations and limitations: First, there is no consistency between the studies cited for inclusion and exclusion criteria. Secondly, there is no consistency or standardization of doses, injectate volumes or types of glucocorticoids utilized for either TFESI or ILESI between studies, or in the case of some studies (11) even between the different approaches used in the same study. There is no standardization of follow-up periods or for number or type of interval treatments, including additional injections, performed in either group. No consensus was identified between the need for addition or lack of addition of local anesthetic to the steroid, or to the type of local anesthetic or dose used, which was disparate in all studies. A standardized approach to the interlaminar space for ILESI and to the intervertebral foramen during TFESI was notably absent. Needle type, gauge, and rate of injection also varied among studies. Statistical methodologies were also applied in a disparate manner in many of the studies which met inclusion criteria.

Conclusion

Based on the 5 randomized, controlled trials consisting of 249 subjects which directly compared TFESI to ILESI for unilateral lumbosacral pain secondary to disc herniation/degeneration, there is high quality evidence to support a finding of no clinically significant difference in efficacy for pain relief or functional improvement between the 2 techniques at all follow-up intervals. This limited sample of studies has potentially profound implications for the clinical practice of interventional pain medicine. Current practice trends have demonstrated a shift away from interlaminar epidural steroid injections, towards the increasingly more widespread practice of the transforaminal approach (17), in part due to the unsubstantiated belief of superior efficacy. This perceived superiority of TFESI is accompanied by potential additional risks, likely to be much less common with ILESI, such as intra-discal and intravascular injection with the attendant sequelae. Additionally, though TFESI and ILESI have been shown in prospective trials to be efficacious for pain relief greater than 6 months (71), there is insufficient direct comparative literature addressing differences in outcomes between the 2 techniques beyond 6-months of follow-up. This begs the question as to whether the increased risk of potential catastrophic morbidity is effectively offset by the minimal differences in efficacy between the 2 respective approaches. While some of the increased risks associated with TFESI may be ameliorated by removal of particulate corticosteroid from the injectate, numerous studies have demonstrated that corticosteroid use itself may have marginal benefit in epidural injections (75-78).

If one elects to choose a neuraxial steroid injection as part of a multi-modal approach to the management of unilateral radicular pain, the risks versus benefits of each approach must be taken into consideration. Although each technique poses its own unique characteristic set of risks, it appears that their efficacy in terms of pain relief or improvement in functioning is not significantly different. Future studies are necessary to confirm the findings of this systematic review, including

larger numbers of subjects and with standardization of approaches, doses, and inclusion/exclusion criteria may help resolve any ongoing controversies involving a comparison of selecting either interlaminar vs. transforaminal administration of corticosteroids for unilateral radicular type pain.

Conflict of Interest

Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

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