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Review Article

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SPINE SECTION

The Effectiveness of Lumbar Transforaminal Injection of Steroid for the Treatment of Radicular Pain: A Comprehensive Review of the Published Data

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Abstract

Objective. To determine the effectiveness of lumbar transforaminal injection of steroid for the treatment of radicular pain. **Design**. Comprehensive systematic review. **Outcome Measures**. The primary outcome of interest was the proportion of individuals with reduction of pain by ≥50%. Additional outcomes of interest were a more-than-two-point reduction in pain score, patient satisfaction, functional improvement, decreased use of pain medication, and avoidance of spinal surgery. **Results**. For patients with disc herniations, using the criterion of ≥50% reduction in pain, success rates across included studies (range) were 63% (58–68%) at one month, 74% (68–80%) at three months, 64% (59–69%) at six months, and 64% (57–71%) at one year. For patients with lumbar spinal stenosis, success rates across included studies (range) were 49% (43–55%) at one month, 48% (35–61%) at three months, 43% (33–53%) at six months, and 59% (45–73%) at one year, but there was a lack of corroboration from appropriately controlled studies. **Conclusions**. There is strong evidence that lumbar transforaminal injection of steroids is an effective treatment for radicular pain due to disc herniation. There is a lack of high-quality evidence demonstrating their effectiveness for the treatment of radicular pain due to spinal stenosis, though small studies suggest a possible benefit. Lumbar transforaminal injection of nonparticulate steroids is as effective as injections with particulate steroids.

Key Words: Lumbar; Radicular pain; Transforaminal; Epidural; Steroid; Injection

Introduction

Lumbar transforaminal injection of steroid (LTFIS) is a treatment for radicular pain. Steroids are believed to have a therapeutic effect due to their anti-inflammatory properties. This belief is supported by evidence from in vitro studies that show that steroids have a role in decreasing inflammatory mediators such as cytokines and chemokines [1,2]; another study suggests that steroids may provide a stabilizing effect on nociceptive signaling in C-fibers and suppression of ectopic neural discharges [3]. Research has demonstrated that patients with radicular pain exhibit elevated levels of the neuro-inflammation marker 18 kDa translocator protein in both the neuroforamina (containing dorsal root ganglion and nerve roots) and the spinal cord [4], and that epidural injection of steroid may help reduce levels of this neuroinflammatory protein [4].

LTFIS is distinguished from other forms of epidural injections by precise injection of corticosteroid in close proximity to the dorsal root ganglion (DRG) and nerve root using radiographic guidance [5]. The presumption

with this targeted delivery technique is that by placing the steroid in close proximity to the affected nerve root and DRG, the therapeutic effect of this agent will be optimized [5].

The present review was undertaken to provide an update of a 2013 systematic review by MacVicar et al., which evaluated published data through 2012 [6], and to provide practicing physicians with information critical to understanding the appropriate indications, risks, safety precautions, and expected benefits of LTFIS in the management of lumbar radicular pain.

Methods

The objective of the literature search was to identify data concerning the effectiveness or complications of LTFIS for the treatment of radicular pain. Relevant studies on LTFIS were obtained by searching the PubMed and EMBASE Drugs and Pharmacology databases, using the following terms: lumbar, lumbosacral, transforaminal, epidural, steroids, and injection. Literature was also identified from the bibliographies of retrieved publications. Publications that were not available in English were eliminated, as were articles that did not provide information relevant to the effectiveness or safety of LTFIS.

Etiology of Radicular Pain

Theoretically, the effectiveness of LTFIS might differ based on the etiologic condition and mechanism(s) causing pain. Studies on the effectiveness of LTFIS were categorized by the diagnosis for which LTFIS was indicated. These diagnostic groups were radicular pain due to disc herniation, radicular pain due to spinal stenosis (including fixed lesions, resulting in central canal, subarticular zone, lateral recess, and neuroforaminal stenosis), and radicular pain due to other diagnoses. The diagnoses were verified by both the descriptions provided by the study authors and the various imaging studies reported in the articles.

Study Design

For evidence of effectiveness, observational, pragmatic, and explanatory studies were included for review. High-quality observational cohort studies were accepted for review on the grounds that such studies provide prima facie evidence of effectiveness. Pragmatic studies were accepted because they 1) demonstrate whether an intervention is more effective than an alternative treatment and 2) provide important information about the effectiveness of the intervention in the same manner as a prospective cohort study. Explanatory trials compare LTFIS with a treatment not expected to have a therapeutic effect; like a cohort study, they provide a measure of the success rate of the index treatment. Explanatory studies also reveal the attributable effect of LTFIS. The attributable effect is the difference in success rates between the index treatment and a sham treatment, which distinguishes the extent to which the index treatment has a therapeutic effect beyond the nonspecific effects of a sham treatment. Commentaries, essays, editorials, systematic reviews, and other publications that did not provide original data were excluded from success rate calculations.

Publications of original data concerning complications were included regardless of study type. Case reports and studies of treatment were included in order to establish the spectrum, nature, and prevalence of possible complications of LTFIS. Articles that reported complications were analyzed to determine if the complication could plausibly be attributed to LTFIS, and thereafter if it was attributable to technical aspects of the injection or to one of the agents injected. Technical complications were also assessed on whether the procedure had been conducted according to guidelines [5,7].

Assessment of Methodological Rigor and Appropriateness of Data Analysis

Four reviewers independently assessed publications on the effectiveness of LTFIS for radicular pain. The reviewers were practicing interventional pain physicians who regularly perform LTFIS. Each holds postgraduate qualifications in interventional pain management and has successfully completed formal certificate courses in evidence-based medicine. Studies were included if they met the following criteria: 1) presentation of clinically relevant data on the efficacy or effectiveness of LTFIS for the treatment of radicular pain *and* 2) presentation of valid information based on appropriate procedural technique, study methodology, and data analyses according to the principles of evidence-based medicine [8] or the ability to perform appropriate data analyses from raw published data; *or* 3) report of a complication associated with LTFIS. Studies that did not contain categorical data or the ability to extract categorical data were excluded. Categorical data analysis defines proportions of patients in which prespecified outcomes (e.g., $\geq$50% pain relief) are achieved—indicating the success rates of the given treatment. Although group data analysis might suggest that a treatment is statistically effective, it does not reveal how frequently the treatment is successful or the degree to which it is expected to be effective for a given patient [8].

Reviewers also evaluated studies for their intrinsic methodological rigor, assessing various factors critical in the assessment of the quality of studies of pain [8], including whether the study used an acceptable technique for LTFIS, if the sample was representative of a realistic clinical population, if validated outcome measures were used, if <20% of patients were lost to follow-up, if the study was controlled for co-interventions, whether there were any conflicts of interest, and whether the diagnostic criteria and assessment tools were valid. Four weeks was considered a minimum threshold for clinically significant

duration of therapeutic effect; studies following patients for less than four weeks postinjection were excluded. Each reviewer provided an appraisal of each paper and discussed conclusions. Elements of data collection methodology were also considered. Prospective studies were considered to be inherently higher quality than retrospective studies with regard to retrieval bias (not all patients are identified and reported). Studies with independent observers were considered to be inherently of higher quality than those without, due to reduced observer and response bias. The results of studies including measures of pain, function, or disability and the use of other health care were considered more convincing than studies reporting only success rates for pain relief. The body of evidence was evaluated using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) system of appraisal to determine the quality of the evidence of the effectiveness of LTFIS [9]. In essence, the GRADE system asks reviewers to evaluate the body of evidence transparently with consideration not only to study design, but also to attributes that would strengthen or weaken confidence in the estimate of effect. GRADE provides an initial rating of quality based upon the best available evidence that comprises the body of knowledge, then further requires consideration of weaknesses (e.g., risk of bias, indirectness) that merit downgrading and strengths (e.g., large magnitude of effect, dose-response gradient) that would justify upgrading the rating of the quality of the body of evidence. The published data on the effectiveness and safety of LTFIS were taken into account, and overall conclusions were drawn in accordance with the GRADE system. With regard to both study inclusion and GRADE evaluation, disagreements were resolved by consensus decision among the reviewers. For acceptable studies that provided categorical data, the success rates and confidence intervals were calculated.

Results

Table 1 shows treatment success rates reported in individual explanatory, pragmatic, and observational studies; the studies are grouped by etiology of radicular pain. Table 2 presents study-defined definitions of treatment success compared with 50% pain reduction as the definition of treatment success, stratified by study design. The literature search yielded 32 observational cohort studies, nine pragmatic trials, and two explanatory trials that met established inclusion criteria for our review.

Radicular Pain Due to Disc Herniation

The majority of studies reported on the clinical outcomes of LTFIS for the treatment of radicular pain due to intervertebral disc herniation. The results are grouped by the type of study.

Observational Cohort Studies

Observational cohort studies that met criteria for inclusion in this review provided evidence on the effectiveness of LTFIS in the treatment of radicular pain caused by lumbar intervertebral disc herniation. Several studies were excluded due to unacceptable study methodology, including inadequate description of LTFIS technique [10], inadequate follow-up [11], or >20% of subjects lost to follow-up [10,12]. One study used a more-than-two-point numeric rating scale (NRS) pain reduction and "at least satisfied with treatment" to define success and reported a success rate of 75% (95% confidence interval [CI] = 64–86%) at two months and 66% (95% CI = 54–78%) at four months [13].

Success, defined as a 50% reduction in radicular pain, was assessed at different time points. As shown in Table 1, observational studies have reported statistically similar success rates at given follow-up periods. At one month, success was 60% (95% CI = 48–72%) [32] in one study and 79% (95% CI = 66–92%) in another (Table 1) [33]. A different study used an 80% reduction in pain to define success and reported a success rate of 67% (95% CI = 55–79%) at one month [37].

At two months, one study defined success as either a 50% reduction in pain or >40% improvement in Oswestry Disability Index (ODI) score. It reported success in 58% of subjects (95% CI = 54–62%) at two months [39]. Other studies, which defined success as >50% NRS reduction, reported success rates of 57% (95% CI = 50–64%) [38] and 66% (95% CI = 51–81%) [13]. The study by Maus et al. included a large number of subjects and reported a success rate at two months that was consistent with those found in controlled trials [38]. Another study reported success rates of 68% (95% CI = 52–84%), 56% (95% CI = 39–73%), and 59% (95% CI = 42–76%) at two, six, and 12 months, respectively [27].

Successful outcomes (defined by either 50% improvement or >30-mm improvement in visual analog scale [VAS] score) were reported in 56% (95% CI = 43–69%) of subjects at three months [40]. Yet another study, which also followed patients for three months, reported that 53% (95% CI = 38–68%) of patients had a >50% reduction in pain [26].

By the same definition of success, another study found a success rate of 75% (95% CI = 65–85%) at six months [25]. When pain relief was maximally defined as 100% relief at six months, 30% (95% CI = 14–46%) of subjects met success criteria [31].

Observational cohort studies demonstrate that symptoms continue to be improved at the one-year mark. There has been speculation that this may represent regression to the mean or be attributable to a favorable natural history of the disease. An older study that defined success as "at least moderate relief of symptoms" demonstrated a success rate of 73% (95% CI = 57–89%) [24]. Another study reported similar success rates of 73%

Table 1. Treatment success rates reported in individual explanatory, pragmatic, and observational studies; the studies are grouped by etiology of radicular pain

References	Definition of Success	Time of Follow-up Assessment	Total No., Success Rate (95% CI)
Radicular pain due to lumbar disc herniation			
Explanatory studies			
Vad et al. 2002 [14]†	Patient satisfaction score of "good" or "very good," ≥5-point RMDQ improvement, and >50% NRS improvement	1 y	Treatment group: 25, 84% (70–98%) Placebo group – saline trigger point injection: 23, 48% (28–68%)
Ghahreman et al. 2010 [15]†	≥50% pain reduction on NRS	1 mo 3 mo 6 mo 1 y	28, 54% (36–72%) 28, 39% (21–57%) 28, 32% (15–49%) 28, 25% (9–41%) Placebo group – intramuscular injection of normal saline: 26, 15% (1–29%)
Pragmatic studies			
Karppinen et al. 2001 [16]	>75% relief of leg pain	1 mo 3 mo 6 mo 1 y	80, 41% (29–53%) 80, 38% (26–50%) 80, 30% (20–40%) 80, 38% (26–50%)
Jeong et al. 2007 [17] ‡	>50% VAS improvement	6 mo	193, 61% (54–68%)
Rados et al. 2011 [18]†	>50% VAS improvement	6 mo	32, 63% (46–80%)
Ghai et al. 2014 [19]†	≥50% VAS improvement	1 mo 3 mo 6 mo 1 y	30, 63% (46–80%) 30, 77% (62–92%) 30, 77% (62–92%) 30, 77% (62–92%)
Gupta et al. 2014 [20]‡	≥50% VAS improvement	1 mo 3 mo	20, 80% (62–98%) 20, 90% (77–100%)
Kennedy et al. 2014 [21]†	≥50% NRS improvement	3 mo 6 mo	78, 73% (63–83%) 78, 74% (64–84%)
Manchikanti et al. 2014 [22]†	≥50% NRS improvement and ≥50% ODI improvement	3 mo 6 mo 1 y 2 y	60, 82% (72–92%) 60, 87% (78–96%) 60, 73% (62–84%) 60, 73% (62–84%)
Pandey et al. 2016 [54]†	≥50% improvement of JOA score	1 y	40, 90% (81–99%)
Observational studies			
Weiner and Fraser 1997 [24]‡	At least "moderate" relief of symptoms	1 y	30, 73% (57–89%)
Lutz et al. 1998 [25]†	>50% NRS improvement	6 mo	69, 75% (65%–85%)
Viton et al. 1998 [26]†	>50% VAS improvement	3 mo	40, 53% (38–68%)
Rosenberg et al. 2002 [27]†	>50% NRS improvement	2 mo 6 mo 12 mo	34, 68% (52–84%) 34, 56% (39–73%) 34, 59% (42–76%)
Wang et al. 2002 [28]†	Avoidance of surgery	1 y	69, 77% (67–87%)
Schaufele et al. 2006 [29]†	Avoidance of surgery	1 y	20, 90% (77–100%)
Yang et al. 2006 [30]†	Avoidance of surgery	2 y	21, 67% (47–87%)
Ackerman and Ahmad 2007 [31]†	100% pain relief	6 mo	30, 30% (14–46%)
Choi et al. 2007 [32]†	>50% VAS improvement and satisfaction score of at least "improved"	1 mo	68, 60% (48–72%)
Lee et al. 2009 [13]†	≥2-point NRS improvement and at least "satisfied" with treatment	2 mo 4 mo	59, 75% (64–86%) 59, 66% (54–78%)
Lee et al. 2009 [33]†	>50% VAS improvement	1 mo 2 mo	38, 79% (66–92%)* 38, 66% (51–81%)*
Mendoza-Lattes et al. 2009 [34]†	Avoidance of surgery	1 y	54, 56% (43–69%)
Manson et al. 2013 [35]†	Avoidance of surgery	6 mo	91, 56% (46–66%)
Van Helvoirt et al. 2014 [36]†	At least "significantly reduced pain" and avoidance of surgery	1 y	71, 76% (66–86%)
Joswig et al. 2016 [37]	>80% VAS reduction	1 mo	57, 67% (55–79%)
Maus et al. 2016 [38]	≥50 NRS improvement	2 mo	175, 57% (50–64%)
Singh et al. 2016 [39]‡	>50% NRS improvement or >40% ODI improvement	2 mo	721, 58% (54–62%)

(continued)

Table 1. continued

References	Definition of Success	Time of Follow-up Assessment	Total No., Success Rate (95% CI)
Tecer et al. 2016 [40]‡	>50% or >30-mm VAS improvement	3 mo	59, 56% (43–69%)
van Helvoirt et al. 2016 [41]†	Avoidance of surgery, ≥50% VAS improvement, ≥50% RMDQ improvement, GPE of at least "satisfaction"	1 y	79, 76% (67–85%)
Sariyildiz et al. 2017 [42]	≥50% VAS improvement	1 y	75, 73% (63–83%)
Radicular pain due to spinal stenosis			
Explanatory studies			
None	N/A	N/A	N/A
Pragmatic studies			
Jeong et al. 2007 [17]‡	>50% VAS improvement	6 mo	46, 57% (43–71%)
Observational studies			
Botwin et al. 2002 [43]†	≥50% VAS improvement	1 y	34, 75% (60–90%)
Rosenberg et al. 2002 [27]†	>50% NRS improvement	2 mo	26, 54% (35–73%)
		6 mo	26, 19% (4–34%)
		12 mo	26, 35% (17–53%)
Lee et al. 2009 [13]†	≥2-point NRS improvement and at least "satisfied" with treatment	2 mo	57, 67% (55–79%)
		4 mo	57, 51% (38–64%)
Lee et al. 2009 [33]†	>50% VAS improvement	1 mo	49, 63% (49–77%)*
		2 mo	49, 53% (39–67%)*
Smith et al. 2010 [44]†	≥50% VAS improvement	1 mo	19, 32% (11–53%)
Ploumis et al. 2014 [45]†	≥50% VAS improvement	6 mo	20, 90% (77–100%)
Park et al. 2015 [46]†	>50% NRS improvement	1 mo; 3 mo	30, 70% (54–86%); 30, 43% (25–61%)
Davis et al. 2016 [47]†	Avoidance of surgery	2 y	68, 68% (57–79%)
Farooque et al. 2016 [48]	≥50% NRS improvement	1 mo	26, 30% (12–48%)
		3 mo	26, 53% (34–72%)
		6 mo	26, 44% (25–63%)
Maus et al. 2016 [38]	≥50 NRS improvement	2 mo	188, 47% (40–54%)
Radicular pain due to failed back surgery syndrome			
Explanatory studies			
None	N/A	N/A	N/A
Pragmatic studies			
None	N/A		
Observational studies			
Rosenberg et al. 2002 [27]†	>50% NRS improvement	2 mo	13, 23% (0–46%)
		6 mo	13, 23% (0–46%)
		12 mo	13, 23% (0–46%)
Rahimzadeh et al. 2014 [49]‡	>50 NRS improvement	1 mo	13, 46% (19–73%)

CI = confidence interval; GPE = global perceived effect; JOA = Japanese Orthopedic Association; LTFIS = lumbar transforaminal injection of steroid; NRS = numeric rating scale; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire; VAS = visual analog scale.

*"Small" LTFIS group: 3 mL of injectate.

†Multiple LTFIS were allowed.

‡Unclear if multiple LTFIS were allowed.

(95% CI = 63–83%) [42], defined by 50% reduction in VAS at one year.

Pragmatic Studies

There were several studies that did not meet criteria for inclusion in the review. Some studies were excluded because they did not include any categorical data or raw data to allow for calculation of success rates [23,34,50]. Others were excluded due to inadequate description of LTFIS technique [51,52] or inadequate duration of follow-up [53].

There were eight pragmatic studies that provided acceptable data on success rates of LTFIS for disc herniation. Most studies used pain relief as the primary outcome. One study defined success as a 50% improvement in Japanese Orthopedic Association score and reported a success rate of 90% (95% CI = 81–99%) at one year [54].

Several studies used ≥50% VAS improvement as the definition of success. Studies variously demonstrated success rates at one month of 63% (95% CI = 46–80%) [19] and 80% (95% CI = 62–98%) [20]. At three months, success rates were 77% (95% CI = 62–92%) [19], 73% (95% CI = 63–83%) [21], and 90% (95% CI = 77–100%) [20]. At six months, success rates were 63% (95% CI = 46–80%) [18] and 74% (95% CI = 64–84%) [21].

One study that compared LTFIS with transforaminal epidural injection of saline defined success as 75% relief of leg pain [16,55]. This study has been categorized as a pragmatic study, as epidural injection of any substance

Table 2. Total No., success rates, and 95% confidence intervals for study-defined definitions of treatment success vs ≥50% pain reduction as the definition of treatment success, stratified by study design type

		Discogenic Radicular Pain				Spinal Stenosis-Related Radicular Pain			
Study Design		Explanatory	Pragmatic	Observational	All	Explanatory	Pragmatic	Observational	All
All definitions of "success" defined by study investigators* ≥50% pain reduction	1 mo	28, 54% (36–72%)	130, 53% (44–62%)	1,123, 58% (55–61%)	1,281, 57% (54–60%)	–	–	312, 49% (44–55%)	312, 49% (43–55%)
	3 mo	28, 39% (21–57%)	268, 67% (61–73%)	158, 59% (51–67%)	454, 65% (61–69%)	–	–	113, 50% (41–59%)	113, 50% (41–59%)
	6 mo	28, 32% (15–49%)	513, 65% (61–69%)	224, 59% (53–65%)	765, 62% (59–65%)	–	46, 57% (43–71%)	52, 31% (18–44%)	98, 43% (33–53%)
	1 y	53, 53% (40–66%)	170, 58% (51–65%)	432, 73% (69–77%)	655, 67% (63–71%)	–	–	46, 59% (45–73%)	46, 59% (45–73%)
	2 y	–	60, 73% (62–84%)	21, 67% (47–87%)	81, 72% (62–82%)	–	–	68, 68% (57–79%)	68, 68% (57–79%)
	1 mo	28, 54% (36–72%)	50, 72% (60–84%)	247, 62% (56–68%)	325, 63% (58–68%)	–	–	312, 49% (43–55%)	312, 49% (43–55%)
	3 mo	28, 39% (21–57%)	128, 78% (71–85%)	40, 62% (47–77%)	196, 74% (68–80%)	–	–	56, 48% (35–61%)	56, 48% (35–61%)
	6 mo	28, 32% (15–49%)	333, 66% (61–71%)	71, 69% (58–80%)	432, 64% (59–69%)	–	46, 57% (43–71%)	52, 31% (18–44%)	98, 43% (33–53%)
	1 y	28, 25% (9–41%)	30, 77% (62–92%)	109, 71% (62–80%)	167, 64% (57–71%)	–	–	46, 59% (45–73%)	46, 59% (45–73%)
	2 y	–	–	–	–	–	–	–	–

*Depending on the study, investigators used various definitions of "success," such as improvements in pain or function, positive satisfaction scores, avoidance of surgery, or combinations thereof.

(i.e., steroid, local anesthetic, saline) has the potential to have a therapeutic effect and therefore cannot be considered a placebo. Success rates of 41% (95% CI = 29–53%) at one month, 38% (95% CI = 26–50%) at three months, 30% (95% CI = 20–40%) at six months, and 38% (95% CI = 26–50%) at one year were observed [16].

Other studies incorporated validated functional assessment tools in defining success. One pragmatic study randomized patients to lumbar transforaminal injection of lidocaine and saline or lumbar transforaminal injection of lidocaine and betamethasone (LTFIS) [22]. The study defined success as ≥50% reduction in pain and ≥50% improvement in ODI. For the LTFIS group, success rates were 82% (95% CI = 72–92%) at three months, 87% (95% CI = 78–96%) at six months, 73% (95% CI = 62–84%) at one year, and 73% (95% CI = 62–84%) at two years. The success rates of the LTFIS group were higher than the lidocaine and saline group, though they failed to reach statistical significance [22].

One high-quality pragmatic study on LTFIS for radicular pain due to disc herniation met inclusion criteria and included patients with both LSS and disc herniation, with data stratified by diagnosis [17]. However, because the study did not compare LTFIS with a conventional control treatment, but compared the outcomes of two different techniques of LTFIS, the study is being categorized as providing observational data for the purposes of this review. At six months, 61% (95% CI = 54–68%) experienced a ≥50% reduction in pain on the VAS [17].

Explanatory Studies

Two explanatory studies met criteria for inclusion [14,15]. Both showed clinically and statistically significant improvement in pain in the LTFIS groups compared with other treatments. A well-designed prospective double-blind randomized controlled trial (RCT) [15] compared the outcomes of 1) transforaminal injection of steroid and local anesthetic (LTFIS), 2) transforaminal injection of local anesthetic alone, 3) transforaminal injection of normal saline, 4) intramuscular injection of steroid, and 5) intramuscular injection of normal saline. Success was defined as ≥50% NRS improvement at one month. A significantly greater proportion of patients treated with LTFIS reported treatment success compared with transforaminal injection of local anesthetic, transforaminal injection of saline, intramuscular steroid injection, or intramuscular saline injection. For the LTFIS group, success rates were 54% (95% CI = 36–72%) at one month, 39% (95% CI = 21–57%) at three months, 32% (95% CI = 15–49%) at six months, and 25% (95% CI = 9–41%) at one year. Significant improvements in function, disability, and reductions in use of other health care were observed in the LTFIS group compared with the other groups (Table 1).

Another RCT compared LTFIS with intramuscular injection of saline [14]. This study used strict criteria of

Table 3. Comparative success rates in studies of particulate vs nonparticulate transforaminal injection of steroids

References	Indication	Definition of Success	Time of Follow-up Assessment	Corticosteroids	Success Rate
Park et al. 2010 [107]†	Lumbar radicular pain	>50% relief of pain	1 mo	Dexamethasone (7.5 mg)	36% (23–49%)
				Triamcinolone (40 mg)	100% (93–100%) No significant differences in disability scores
El-Yahchouchi et al. 2013 [106]*	Radicular pain with or without radiculopathy	≥50% relief of pain ≥40% RMDQ improvement	2 mo	Dexamethasone (10 mg)	Pain: 52.3% (45.9–58.8%) Function: 46.4% (39.9–52.8%)
				Triamcinolone (80 mg)	Pain: 45.0% (41.5–48.5%) Function: 41.5% (38.0–45.0%)
				Bethamethasone (12 mg)	Pain: 43.6% (40.6–46.6%) Function: 37.2% (34.3–40.1%) Success rates were not significantly different between groups
Kennedy et al. 2014 [21]*	Lumbar radicular pain for disc herniation	≥50% reduction in NRS >50% reduction in ODI	3 mo 6 mo	Dexamethasone (10 mg)	3 mo Pain: 73% (59–87%) ODI: 68% (54–82%) 6 mo Pain: 73% (59–87%) ODI: 71% (57–85%)
				Triamcinolone (40 mg)	3 mo Pain: 73% (59–87%) ODI: 68% (53–83%) 6 mo Pain: 76% (62–90%) ODI: 65% (50–80%) No significant differences between groups found for relief of pain, functional improvement, or rates of surgery
Denis et al. 2015 [68]*	Lumbosacral radicular pain	≥50% pain relief	3 mo	Dexamethasone (7.5 mg)	59% (41–77%)
				Betamethasone (6 mg)	33% (15–51%) No significant differences between mean pain scores at all follow-up points ($P = 0.058$)
Kim et al. 2016 [108]*	Excluded from success rate analysis due to grouped diagnoses and inclusion of data from interlaminar injections not separated from LTFIS data	Relative satisfaction	6-mo phone follow-up	Triamcinolone (40 mg) Dexamethasone (10 mg)	Relative satisfaction was significantly better with triamcinolone than with dexamethasone, and the injection-free interval after injection was significantly longer with triamcinolone than with dexamethasone
Bensler et al. 2018 [109]†	"Lumbar radiculopathy" without diagnostic criteria	"Better" or "much better" on Patients' Global Impression of Change scale	1 mo questionnaire	Dexamethasone (4 mg)	33% (26–40%)
				Triamcinolone (40 mg)	44% (39–49%) Significantly greater improvement in the triamcinolone group ($P = 0.019$) More patients reported they were "better" or "much better" in the triamcinolone group

LTFIS = lumbar transforaminal injection of steroid; NRS = numeric rating scale; ODI = Oswestry Disability Index; RMDQ = Roland Morris Disability Questionnaire.

success, including a patient satisfaction score of "good" or "very good," a five-or-more-point Roland Morris Disability Questionnaire (RMDQ) improvement, and ≥50% NRS improvement. The responder rate was significantly higher in the LTFIS group compared with the intramuscular saline injection group ($P < 0.005$). At one year, the success rate in the LTFIS group was 84% (95% CI = 70–98%). The shortcomings of this study included lack of blinding.

GRADE Assessment of the Evidence: High Quality

Multiple randomized controlled trials and high-quality observational studies have provided high-quality evidence supporting the effectiveness of LTFIS in reducing pain, improving function, and reducing reliance on other health care in patients with radicular pain due to disc herniation.

Radicular Pain Due to Spinal Stenosis

Few high-quality studies evaluating LTFIS specifically for radicular pain due to lumbar spinal stenosis (LSS) were encountered; however, a number of cohort and pragmatic studies met criteria for inclusion in this review.

Observational Cohort Studies

Several studies used pain relief as their primary outcome measure (Table 1). Less convincing definitions of success were used in some studies. These definitions of success included more-than-two-point NRS improvement and a patient satisfaction rating of "at least satisfied." Using these criteria, success rates were 67% (95% CI = 55–79%) and 51% (95% CI = 38–64%) [13] at two and four months, respectively.

The proportion of patients with a successful outcome, defined as ≥50% reduction in VAS or NRS, was used in several studies. At one month, success rates were reported as 30% (95% CI = 12–48%) [48], 32% (95% CI = 11–53%) [44], 63% (95% CI = 49–77%) [33], and 70% (95% CI = 54–86) [46]. Two-month success rates were reported as 47% (95% CI = 40–54%) [38], 53% (95% CI = 39–67%) [33], and 54% (95% CI = 35–73%) [27]. At three months, success rates were reported as 43% (95% CI = 25–61%) [46] and 53% (95% CI = 34–72%) [48]. At six months, reported success rates were highly variable, reported as 19% (95% CI = 4–34%) [27], 44% (95% CI = 25–63%) [48], and 90% (77–100%) [45]. Although studies that reported success rates at one year showed a high proportion of successful outcomes, these outcomes are inconsistent and may have been related to other factors such as natural history. Defined as ≥50% NRS improvement, successful outcomes at one year were reported as 35% (95% CI = 17–53%) [27], 75% (95% CI = 60–90%) [43], and 90% (95% CI = 77–100%) [45].

Pragmatic Studies

Several studies were excluded due to unacceptable study methodology. Two studies were excluded due to lack of categorical data [56,57]. A large pragmatic study concluded that epidural steroids were ineffective for spinal stenosis, but the study failed to control for or provide subgroup analysis of dose or technique (i.e., interlaminar epidural steroid injection or LTFIS) [58]. It is also unclear which patients had radicular pain symptoms vs neurogenic claudication alone, two conditions that likely respond differently to LTFIS.

One high-quality pragmatic study on LTFIS for radicular pain due to LSS met inclusion criteria and included patients with both LSS and disc herniation, with data stratified by diagnosis. However, because the study did not compare LTFIS with a conventional control treatment, but compared the outcomes of two different techniques of LTFIS, the study is being categorized as providing observational data for the purposes of this review. Defining success as a ≥50% VAS reduction in pain, the study demonstrated a success rate of 57% (95% CI = 43–71%) at six months [17].

GRADE Assessment of the Evidence: Low Quality

With an evidence base consisting of studies with conflicting results related to the effectiveness of LTFIS in the treatment of LSS, the quality of evidence is low in accordance with the GRADE system. Additional studies, controlled for technique and dose and with appropriate subgroup analysis by specific type of stenosis (subarticular, central, foraminal), would assist in determining whether LTFIS is an effective treatment for patients with radicular pain due to lumbar spinal stenosis.

Other Diagnoses

Some studies evaluated mixed diagnostic categories or evaluated miscellaneous conditions such as radicular pain due to failed back surgery syndrome or epidural lipomatosis.

Observational Cohort Studies

LTFIS has been used to treat radicular pain in patients with epidural lipomatosis, "mixed radicular pain," and failed back surgery syndrome, among other etiologies, but evidence on effectiveness is less than convincing because of small sample sizes, short follow-up, or low success rates. Several studies were excluded due to unclear diagnosis or for reporting outcomes of LTFIS for mixed diagnoses. When results were not separated by diagnosis, the studies were omitted from this review [23,59–61]. Others were excluded for not adequately describing technique [62] or for inconsistent follow-up [60]. One study suggested a potential benefit of LTFIS for radicular pain resulting from degenerative lumbar spondylolisthesis, but it was excluded due to the absence of categorical data [63]. Small case series have reported successful relief of

radicular pain from epidural lipomatosis [64,65]. A case series of patients who had persistent radicular pain six months after lumbar discectomy and fusion reported improvement after LTFIS [33]; however, the diagnosis that precipitated the surgery was unclear. One study examined the impact of adding hyaluronidase or saline to LTFIS for patients with the vague diagnosis of "failed back surgery syndrome" [49]. The LTFIS outcomes in this study showed success rates of 46% (95% CI = 19–73%) at four weeks. Another study defined success as a >50% improvement in NRS and reported a success rate of 23% (95% CI = 0–46%), which remained consistent at two, six, and 12 months [27].

Pragmatic Studies. No pragmatic studies met inclusion criteria. Several studies were excluded due to unclear diagnoses [66–71]. One study compared response rates to LTFIS among various diagnostic groups (LSS, lumbar disc herniation, postsurgery) and reported that there was no significant difference in response [72]. However, categorical data were not presented separately for each diagnosis; therefore, the study was excluded. Another study evaluating dexamethasone vs betamethasone for mixed diagnoses (LSS and disc herniation) found no difference between the two drugs but was excluded because data were not stratified by diagnosis [68].

GRADE Assessment of the Evidence: Low Quality. With low-quality and very limited evidence regarding the effectiveness of LTFIS for radicular pain due to diagnoses other than disc herniation or LSS, the quality of evidence is low in accordance with the GRADE system. Additional studies with appropriate subgroup analysis by specific diagnosis would assist in determining whether LTFIS is an effective treatment for patients with radicular pain due to other diagnoses.

Dose

Studies have attempted to identify the lowest effective dose of steroid to use in LTFIS. One study, which showed that at one week responses to LTFIS with 10 mg, 20 mg, and 40 mg of triamcinolone were superior to a 5-mg dose, was excluded from analysis due to inadequate duration of follow-up [73]. Another study examined dexamethasone injections of 4 mg, 8 mg, and 12 mg for mixed diagnoses causing "radicular pain" [74]. This study showed no difference among the different doses at 12 weeks; however, accurate conclusions about success rates cannot be drawn due to the diagnostic heterogeneity within the groups of patients. As such, there is currently a lack of high-quality data comparing the relative effectiveness of different steroid doses for LTFIS.

Predictors of Success

Response rates to LTFIS are variable. Many authors have sought to identify patient characteristics that may correlate with the success or failure of the procedure. One study suggested that longer duration of pain symptoms before LTFIS for disc herniation may be associated with poorer outcomes, but more evidence is needed to confirm this observation [25]. Another study showed that pain sensitivity questionnaires did not predict outcomes of LTFIS in patients with radicular pain due to LSS, but it was excluded due to the absence of categorical data [75]. Similarly, a study suggests that early response to LTFIS may predict longer duration of effect, but it was also excluded from the review due to lack of categorical data [23]. With regard to radiographic predictors of success, no study followed patients long enough to define the relationship between magnetic resonance imaging (MRI) characteristics of lumbar disc herniations and long-term LTFIS outcomes [32,38,76]. One study reported that the group with the highest proportion of responders at two weeks included those patients whose imaging exhibited grade 3 nerve compression, followed by grade 2, grade 4, and grade 1 [18]. Another study examined whether MRI features (including segmental level, location, and morphological features of disc herniation, cross-sectional area of disc herniation, and grade of nerve root compression) were predictors of success from LTFIS [76]. This study found that the only clinical feature that predicted a successful outcome after LTFIS was low grade of nerve root compression, which predicted a higher rate of success than high-grade nerve root compression. One study correlated positive findings of lumbar radiculopathy on electrodiagnostic studies, with or without active denervation, with a more favorable outcome from LTFIS [77]. The drawbacks of this study include the fact that electrodiagnostic testing may confirm a diagnosis of radiculopathy, but this test is not sensitive to changes in small nerve fibers that mediate nociception in the case of radicular pain without radiculopathy. At this time, available evidence does not support the use of electrodiagnostic testing to select patients for LTFIS. Radicular pain is primarily evaluated by history, physical examination, and diagnostic imaging.

Surgery-Sparing Effects of LTFIS

Several studies have reported reduced rates of surgery following LTFIS, and several studies have reported successful outcomes from LTFIS when performed on patients who were selected from surgical waiting lists, for whom surgery would have been performed if the procedure was unsuccessful. One well-designed randomized controlled study showed no difference in surgery rates between patients treated with intramuscular steroids and LTFIS, though a higher percentage of patients treated with LTFIS who canceled their surgery reported that they did so because of the beneficial effect of the injection [15]. One study compared transforaminal bupivacaine with LTFIS. At follow-up times of 13 to 24 months, the LTFIS group underwent surgery at a significantly lower rate

[72]. Another study strictly defined success as avoidance of surgery, ≥50% VAS improvement, ≥50% RMDQ improvement, and a patient satisfaction score of at least "satisfaction" [41]. This study reported a success rate of 76% (95% CI = 67–85%) at one year. At six months, one study reported a 56% (95% CI = 46–66%) rate of surgery avoidance [35]. At one year, avoidance of surgery has been reported to vary between 56% and 90% [28,29,36,50]. At two years, 67% (95% CI = 47–87%) [30] and 68% (95% CI = 57–79%) [47] surgery avoidance rates have been reported. The effect of disc morphology on surgery avoidance is unclear, though one study demonstrated a higher rate of surgical avoidance in cases of contained but not extruded disc herniations [16].

Complications

Reports of unusual transient effects postprocedure include singultus (hiccups) [78], oculomotor nerve palsy [79], and perineal pruritis [80]. Technical problems have also been reported, including dural puncture [81] and unintended injection into a vein [82] or disc [83–86]. None of these cases resulted in permanent effects. The risk of epidural hematoma after LTFIS remains low. There is a report of epidural hematoma secondary to a hemorrhagic facet cyst after LTFIS in a patient who had stopped Plavix and aspirin seven days prior [87]. The implications of this case are unclear.

The most significant complication that has been associated with LTFIS is spinal cord infarction, which has been reported in a total of at least 14 cases [88–94]. All of these cases except one [88] involved the use of particulate steroid. The circumstances of that case of spinal cord injury after LTFIS with preservative-free dexamethasone are vague, and without intraoperative images confirming needle placement, the complication cannot be attributed to the injectate [88]. One theory on the etiology of spinal cord infarction after LTFIS with particulate steroids is that spinal cord infarction may arise when particulate steroids are unintentionally injected into an artery that partially supplies the distal spinal cord, leading to embolic infarction either related to the particulate steroid matter itself or agglutination of red blood cells due to speculation caused by the particulate steroid [95–99]. Animal studies demonstrate that nonparticulate steroid injected directly into the vertebral artery causes no measurable neurologic injury [100]. One caveat is that dexamethasone sodium phosphate combined with ropivicaine may result in crystallization of the solution [101]; therefore, that particular combination of medications should be avoided. Several measures, which are outlined in the 2013 Spine Intervention Society Practice Guidelines, can be adopted to reduce the risk of spinal cord infarction [5]. Injection of contrast medium under real-time fluoroscopy should be performed before injection of steroid in order to detect inadvertent vascular injection and reduce the risk of spinal cord infarction. Other measures that can be adopted include digital subtraction angiography and a test dose of a rapidly acting local anesthetic [5].

Large studies have continued to support the safety of LTFIS. A study of >14,000 procedures showed no neurologic, hemorrhagic, or infection-related complications, with vasovagal reactions (1.2% of cases) being the most common "side effect" [102]. Other, mostly minor, transient symptoms after LTFIS have included headache, postprocedure pain, facial flushing, rash, leg weakness, erectile dysfunction, dizziness, increased blood sugar, and hypertensive episodes [103–105]. These are temporary phenomena that might be encountered with any injection involving corticosteroids.

GRADE Assessment of the Evidence of Risks with LTFIS: Very Low Quality

When attempting to apply GRADE to assess the quality of the evidence regarding the risks of LTFIS, it is noted that the published evidence consists of case reports. Accordingly, the body of evidence is of very low quality. With a large study of >14,000 procedures documenting no neurologic, hemorrhagic, or infection-related complications, we have some confidence that the prevalence of complications is very low; however, when they do occur, they can be catastrophic.

Efficacy of Particulate vs Nonparticulate Steroid

One of the most significant areas of new research addresses the comparative effectiveness of particulate vs nonparticulate steroids used in LTFIS. Interest in this area of study is due to the association between LTFIS and ischemic spinal cord infarction, thought to result from embolization of particulate steroid and/or agglutination of red blood cells in the presence of particulate steroid, with subsequent interruption of arterial supply to the spinal cord.

Given the superior safety profile of nonparticulate steroids, many studies have sought to determine whether LTFIS with nonparticulate steroids is inferior to LTFIS with particulate steroids. Four studies have established that nonparticulate steroids are not inferior to particulate steroids for the treatment of pain attributed to disc herniation [21,68,106,107] (Table 3). One study showed no significant difference in the categorical response rate between LTFIS with triamcinolone (particulate steroid) vs dexamethasone (nonparticulate steroid); at six months, >70% of subjects in both groups achieved ≥50% pain reduction [21]. In that study, a greater number of LTFIS procedures were required in the dexamethasone group compared with the triamcinolone group in order to maintain adequate pain relief during the study period ($P < 0.05$) [21]. A fifth study on radicular pain due to heterogeneous etiologies of LSS and disc herniation also showed noninferiority of nonparticulate steroids, but it was excluded from analysis of success rates due to lack of stratification by diagnosis (Table 3) [108]. There was

only one study that demonstrated superiority of particulate compared with nonparticulate steroid [109]. This study, which used subjective "improvement" as the primary outcome measure, reported a greater-frequency "improvement" in the particulate group at one week and one month following LTFIS. The quality of this study was downgraded due to the imprecision of the diagnostic inclusion parameters.

Discussion

The focus of the present review was to analyze the published literature on the effectiveness and safety of LTFIS for the treatment of radicular pain in a rigorous and comprehensive manner. To achieve this goal, studies were analyzed only by researchers fully trained and certified in the application of principles of evidence-based medicine. Studies were selected for inclusion using criteria recommended by established guidelines [8,110].

The recommendations for importance of categorical data analyses have been well documented in medical literature. A panel of leading authorities in pain medicine published their recommendations, known as the "Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials" (IMMPACT) guidelines, recommending categorical data analysis (anchor-based methods) over group (mean) data analysis (distribution-based methods) [110]. Although group data may provide a statistical indication that a treatment is effective, they do not provide any information on the proportion of patients in which the treatment is effective, the number of patients for which it is effective, or the degree of effectiveness in a particular patient.

When assessing the level of evidence in accordance with GRADE and stratifying by underlying pathology, trends do emerge. In this review, the authors encountered observational cohort studies, pragmatic RCTs, and explanatory RCTs. The two high-quality explanatory RCTs that examined LTFIS demonstrated that LTFIS is not a placebo and had a significant lasting benefit over sham treatments. Substantial high-quality observational studies further strengthen the conviction that this treatment has an important role in the treatment of radicular pain. The available data establish LTFIS as an effective treatment for radicular pain. Because there is strong evidence from explanatory studies, the quality of evidence is rated as "high" for the effectiveness of LTFIS for the treatment of radicular pain due to intervertebral disc herniation. Without explanatory studies or appropriate justifications to upgrade the level of evidence due to the magnitude of health effect or dose-response gradient, the quality of evidence is rated as "low" for the effectiveness of LTFIS for the treatment of lumbar radicular pain due to spinal stenosis and other diagnoses such as epidural lipomatosis. Some outcome studies suggest that there is a benefit, but there are no corroborating studies or appropriately controlled studies at this time. Although the quality of evidence is low, this does not indicate that the treatment is ineffective, only that the quality of available evidence in support of LTFIS for these indications is low. The current body of literature does support the conclusion that LTFIS may provide short-term relief of radicular pain related to these diagnoses. An important limitation of the majority of the literature pertaining to spinal stenosis is that the exact nature of "spinal stenosis" was not defined (i.e., central canal, subarticular zone, or neuroforamen). Future studies would be improved by delineating the exact type of stenosis (central, subarticular, or neuroforaminal) and clarifying the distinction between fixed stenosis vs intermittent neurogenic claudication.

The reported surgery-sparing effect of LTFIS is suggested by the evidence, but further study is needed. To confirm that a treatment eliminates the need for surgery, it requires that all patients were destined for surgery and would have had surgery if LTFIS did not work.

LTFIS success rates were higher in patients with a shorter duration of pain, an early positive response to injection, and positive findings of radiculopathy on electromyogram. In terms of radiographic findings, there is little convincing evidence as to whether any MRI disc characteristics predict LTFIS outcomes, though there is some evidence that patients with a low degree of nerve root compression may respond more quickly than patients with a high degree of compression.

The duration of relief after LTFIS is variable. In most of the cases reported in the literature, only one LTFIS treatment was needed for a successful outcome. If the patient's pain is relieved but returns after a period of time, relief can be achieved again by repeat treatment. However, there are known possible systemic side effects of epidural corticosteroid injections, so injections should be limited to the lowest effective dose and number of injections with an appropriate time interval between injections. Most studies included in our review showed a treatment benefit lasting three to six months, with some studies suggesting a benefit at one or even two years post-injection. The rationale for a one- to two-year benefit from LTFIS is likely related to the favorable natural history of lumbar radicular pain, rather than a one- to two-year effect directly related to the corticosteroid. In addition, many studies were not fully controlled for co-interventions. This includes a possibly significant methodological limitation in studies where several LTFIS procedures were performed in the same patient in between follow-up intervals. Although repeated LTFIS procedures may be justified in some cases for added benefit, performing an additional LTFIS procedure without discrete reporting of when the injection(s) occurred creates a challenge in interpreting the true durability of effect of an individual LTFIS. For patients with disc herniation, LTFIS with nonparticulate steroids are as effective as LTFIS with particulate steroids. Five studies demonstrated that nonparticulate steroids are not inferior to particulate

steroids for treatment of radicular pain attributed to intervertebral disc herniation [21,68,106–108].

In addition, data suggest that LTFIS is a safe procedure. Large studies have continued to support the safety of this procedure, with vasovagal reactions as the most common "complication." Prior reports of spinal cord infarctions were associated with use of particulate steroid, which is no longer recommended as a firstline medication. Precautions to improve safety have been documented in the literature [5,7,111]. Particulate steroids were most strongly associated with a risk of spinal cord infarction, thought to be the result of arterial embolization by steroid particles. Particles may also form due to crystallization with combinations of ropivacaine and dexamethasone sodium phosphate, so this particular combination should be avoided [101]. Nonparticulate steroids (not mixed with ropivicaine) should be the firstline choice of medication due to their enhanced safety profile, particularly given the fact that multiple studies have shown nonparticulate steroids to be noninferior to particulate steroids.

There are several general limitations to the present review. It is possible that we did not capture all relevant data. Useful data may have been rejected on the basis of not being available in English. Reviewers are also susceptible to confirmation bias, and their assessments can be influenced by their previous experience with and knowledge of a procedure and its effects.

Conclusions

The published evidence establishes that when appropriate inclusion criteria are applied, LTFIS is an effective treatment for radicular pain due to intervertebral disc herniation. Strong evidence supports this statement. There remains a lack of high-quality evidence demonstrating the effectiveness of LTFIS for the treatment of radicular pain due to spinal stenosis, though the available low-quality data support a possible benefit. There is a paucity of data for miscellaneous conditions such as epidural lipomatosis and failed back surgery syndrome. Published data demonstrate that LTFIS with nonparticulate steroids are not inferior to LTFIS with particulate steroids. Nonparticulate steroids should be the firstline choice of medication due to their enhanced safety profile. More research is needed to identify patient-specific factors that predict the likelihood of a positive response to LTFIS.

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