EFFICACY OF TRANSFORAMINAL EPIDURAL STEROID INJECTIONS IN SYMPTOMATIC SPONDYLOLISTHESIS: A SYSTEMATIC REVIEW

A Major Paper Presented

by

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EFFICACY OF TRANSFORAMINAL EPIDURAL STEROID INJECTIONS IN SYMPTOMATIC SPONDYLOLISTHESIS: A SYSTEMATIC REVIEW

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Abstract

Spondylolisthesis is a known source of chronic back pain due to spinal nerve root compression (Kraiwattanapong et al., 2014). It affects up to 8% of the adult population and is associated with disability, emotional distress, anxiety, and depression (Bouras & Korovessis, 2015; Kreiner et al., 2016; Hsu et al., 2019). Transforaminal epidural steroid injections (TFESI) allow precise delivery of corticosteroids to affected spinal nerves resulting in decreased inflammation and pain (Morgan & Mikhail, 2013). The purpose of this systematic review was to evaluate the efficacy of TFESI as method of pain management in symptomatic lumbar spondylolisthesis. A detailed search was conducted using CINAHL Plus, Google Scholar, Medline, and PubMed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) framework guided this systematic review. Critical Appraisal Skills Programme (CASP) checklists were used to evaluate article reliability. Data extracted from included studies focused on purpose, design, sample, method, limitations, steroid administered, number of injections, follow up interval, and pain scores. Study demographics, outcomes, and cross-sectional analysis tables were created to facilitate the interpretation of collected data. This systematic review concluded that further statistically significant research is needed to confirm the efficacy of TFESI in treating spondylolisthesis related radiculopathy.

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Efficacy of Transforaminal Epidural Steroid Injections in Symptomatic Spondylolisthesis: A Systematic Review

Background/Statement of the Problem

Activity-limiting chronic lower back pain has a worldwide lifetime prevalence of 39% (Deyo et al., 2014). Spondylolisthesis affecting the lumbar spine is a known cause of lower back pain (Veritas Health, 2020). Spondylolisthesis occurs when a vertebra slides forward over the vertebra beneath it (Sencan et al., 2017). This slippage may be secondary to a pars interarticularis defect or degenerative changes (Sencan et al., 2017). The resulting vertebral displacement leads to spinal stenosis, neuroforaminal stenosis, and/or spinal nerve compression (Kraiwattanapong et al., 2014). The accumulative neuro-orthopedic changes manifest as aching pain, radicular pain, paresthesias, muscle fatigue, and weakness affecting the lower back, buttocks, and/or lower extremities (Veritas Health, 2020). Current non-surgical treatment modalities include medical management, physical therapy, and chiropractic evaluation. When these interventions are unsuccessful in controlling lower back pain, epidural steroid injections are typically the next line of treatment offered before surgical intervention (Kraiwattanapong et al., 2014). The purpose of this systematic review is to evaluate the efficacy of transforaminal epidural steroid injections as method of short- and long-term radicular pain management in spondylolisthesis.

Literature Review

This literature review was conducted using CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus, Medline, and PubMed. Search terms used independently and in combination included: spondylolisthesis, epidural steroid injection, epidural, nerve block, corticosteroids, transforaminal, lumbosacral, radiculopathy, radicular pain, and complications. The search was restricted to studies published between 2009-2020.

Spondylolisthesis

Spondylolisthesis is defined as the anterior translation of one vertebra relative to the next caudal segment (Kreiner et al., 2016). Two major subtypes of spondylolisthesis include degenerative spondylolisthesis (DS) and isthmic spondylolisthesis (IS). Degenerative spondylolisthesis occurs secondary to degenerative changes involving the posterior facet joints and/or intervertebral disc and most often occurs at the L4-L5 level. Isthmic spondylolisthesis results from a defect in the pars interarticularis (spondylolysis) and most often presents at the L5-S1 level (Kalichman et al., 2009). A spondylolisthesis diagnosis is confirmed with radiographic imaging documenting the vertebral slip and an abnormality in the pars interarticularis or facet joints (Kalichman et al., 2009). The incidence of spondylolisthesis in the adult population ranges from 3.7% and 8% with a 2:1 male to female gender ratio (Bouras & Korovessis, 2015; Kreiner et al., 2016). Isthmic spondylolisthesis is more common in young adults, adolescents, and athletes (Ferrari, Costa & Fornari, 2012). The defect is bilateral in 80% of cases and unilateral in 20% of cases (Bouras & Korovessis, 2015). Kalichman et al. (2009) conducted a cross-sectional study consisting of 188 participants (104 male and 84 female) to determine the

prevalence of both IS and DS and spondylolysis. The small sample size was identified as a limit to the study. The presence of spondylolysis and spondylolisthesis was confirmed by CT imaging according to protocols derived from Meyerding classification. Images were evaluated blindly in regard to clinical and personal information. Intra-rater reliability was regularly assessed by inserting a repeated "reliability" scan every 10 images. Spondylolysis was identified in 11.5% of participants, 19 of which had bilateral defects. Spondylolisthesis was present in 20.7% of participants and 79% of participants with bilateral spondylolysis had associated spondylolisthesis. The prevalence of IS was 8.2%, 10.6% were male and 5% were female. DS was found in 13.6% of participants, 7.7% were male and 21.3% were female.

Spinal nerve roots pass through the vertebral neuroforamen and divide into the ventral ramus and dorsal ramus which provide motor and sensory nerve innervation (Gegel, Floyd IV, & Hart, 2019). The ventral ramus supplies the anterior body, upper extremities, and lower extremities while the dorsal ramus innervates the posterior body, skin, and back (Gegel, Floyd IV, & Hart, 2019). Vertebral displacement occurs as the superior vertebra slips forward in spondylolisthesis which causes spinal stenosis and narrowing of the neuroforamen (Gegel et al., 2019).

The resultant compression of the spinal nerve at the dorsal root triggers an inflammatory response that disrupts sensory and motor nerve conduction and leads to radicular pain (Gegel et al., 2019). Lumbar radicular pain, also known as neuropathy, nerve pain, or sciatica, is often characterized as burning, or sharp, and may or may not involve numbness and paresthesias (Gegel et al., 2019). The vast majority of adult

patients with symptomatic spondylolisthesis present with back pain and at least half present with radicular lower extremity pain (Kreiner et al., 2016).

Spondylolisthesis directly impacts patient well-being and quality of life. In a cross-sectional study, Hsu et al. (2019) investigated disability, emotional distress, and well-being among 133 patients diagnosed with lumbar spondylolisthesis. The authors utilized a demographic questionnaire, Numeric Rating Scale (NRS), Charlson Comorbidity Index (CCI), Oswestry Disability Index (ODI), State-Trait Anxiety Inventory State (STAI-S), Center for Epidemiological Study-Depression (CES-D), and Psychological Well-Being Scale (PWB). Correlation among the variables and psychological well-being were examined using Pearson's correlation coefficient and multiple linear regression. Forty-two patients (31.6%) reported depression while 86 (64.6%) experienced moderate to severe anxiety. Physical and mental health levels were also low among the group. The authors concluded that the disability, emotional distress, anxiety, and depression associated with lumbar spondylolisthesis negatively impacted patient well-being.

Conservative management is the mainstay of treatment for spondylolisthesis (Kalichman & Hunter, 2008). Initial courses of action include oral medications, physical therapy, acupuncture, and lifestyle modification (Kalichman & Hunter, 2008; Benoy & Azari, 2011). Typically, treatment begins with a 24–48-hour rest period in combination with anti-inflammatory medications (Kalichman & Hunter, 2008). If NSAIDs are prescribed in the elderly population it is critical to monitor for gastrointestinal side effects, bleeding, and cardiovascular effects if COX-2 inhibitors are prescribed (Kalichman & Hunter, 2008). If there is little improvement following two weeks of

treatment physical therapy is warranted (Kalichman & Hunter, 2008). If physical therapy fails to improve symptoms after four to six weeks epidural steroid injections (ESI) may be indicated (Kalichman & Hunter, 2008; Benoy & Azari, 2011).

Epidural Steroid Injections

The first documented use of ESI occurred in Europe in 1952 (Gegel et al., 2019). By 1960 three distinct approaches to these injections had been developed: interlaminar, caudal, and transforaminal (Benoy & Azari, 2011). Since then, ESI utilization has continued to grow. Epidural steroid injections are one of the most commonly performed interventions in the management of chronic lower back pain (Buenaventura, Datta, Abdi, & Smith, 2009). In the United States, more than 1.3 million epidural glucocorticoid injections were performed in approximately 426,000 patients age 65 and older in the year 2013 (Racoosin et al., 2015). In the same year 604,000 U.S. patients less than 65 years of age received at least one ESI (Racoosin et al., 2015).

Epidural steroid injections reduce the painful inflammatory effects associated with nerve root compression and spinal stenosis seen in spondylolisthesis (Benoy & Azari, 2011; Morgan & Mikhail, 2013). Clinical improvements are correlated with the reduction of spinal nerve root edema (Morgan & Mikhail, 2013). Superior results are associated with corticosteroid injection rather than local anesthetic alone (Morgan & Mikhail, 2013). Addition of opioids to the injection was found to offer no greater improvement in outcomes and increased the risk for complications (Morgan & Mikhail).

Buenaventura et al. (2009) conducted a systematic review to evaluate the efficacy of TFESIs in managing lumbar (lower back) and sciatica (leg) pain. The primary outcome measures were short term (up to 6 months) and long-term pain (greater than six months)

relief. Secondary outcome measures consisted of improvement in functional status, psychological status, ability to return to work, and reduction in opioid intake. Article quality was evaluated based on Cochrane and AHRQ criteria and only included patients with at least three months of lower back and lower extremity pain. Of the selected articles two cited the treatment of pain related to lumbar radiculopathy, one cited spinal stenosis, and one nerve compression. Limits of the study relate to the inconsistencies among the class of steroid utilized, exclusion criteria, and selection of pain scales. Researchers found that epidural steroid injections had the ability to reduce pain by 64% to 81%, disability by 60% to 63%, and depression by 56%. Transforaminal epidural steroid injections provide a significant reduction in radicular lumbar pain when compared with no treatment and conservative treatment without TFESIs (Buenaventura et al., 2009). The indicated evidence according to USPSTF guidelines is Level II-1 for short-term pain relief and Level II-2 for long term pain relief while the recommendation according to Guyatt et al.'s criteria is 1C/strong (Buenaventura et al., 2009).

Benoy and Azari (2011) conducted a systematic review to evaluate the efficacy of ESIs using the transforaminal approach in the treatment of radiculopathy caused by spinal nerve impingement or spinal stenosis. A total of 10 randomized trials, four retrospective studies, and nine prospective studies were evaluated. Patients suffering from radicular back pain with radiographic evidence of spinal stenosis or disc herniation served as inclusion criteria. Of the studies selected for this review three evaluated transforaminal epidural steroid injections (TFESI) in patients with spinal stenosis and five with nerve root compression. The quality of the articles was evaluated using Agency for Healthcare Research and Quality standards (AHRQ). Randomized clinical trials required a score of

at least four out of a possible seven for inclusion and observational studies required a three out of a possible five. The primary outcome measure of the study was pain relief. Cases where TFESIs were more effective in pain relief than the controlled treatment constituted a positive outcome in randomized controlled trials. In observational studies, a positive outcome was defined as a positive correlation between TESI and pain relief. Long term pain relief was defined as relief lasting beyond three months and short-term pain relief as less than three months. This systematic review found that TFESIs are effective in managing radicular pain caused by nerve root irritation due to spinal stenosis or lumbar herniation with a high level of confidence (Benoy & Azari, 2011).

Corticosteroids and Inflammation

Synthetic corticosteroids actively control pain through their effects on the inflammatory process and pain signal transduction and transmission (Benoy & Azari, 2011; Nagelhout & Plaus, 2014). They maintain microcirculation at the site of inflammation through reduction of capillary endothelial permeability, prevention of edema, and immune response modulation (Gegel et al., 2019). Corticosteroids interfere with the inflammatory chain reaction through the inhibition of phospholipase found in injured nerves (Gegel et al., 2019; Kraiwattanapong et al. 2014). Phospholipase is a key enzyme in the production of prostaglandins via the cyclooxygenase pathway and leukotrienes via the lipoxygenase pathway (Gegel et al., 2019). When injected epidurally corticosteroids block the transmission of nociceptive c-fibers, which are responsible for neuropathic pain (Roy et al., 2011; Nagelhout & Plaus, 2014). They also provide direct membrane stabilization through the suppression of ectopic firing of nociceptors related to nerve injury (Nagelhout & Plaus, 2014).

Particulate and Nonparticulate Steroids

There are multiple synthetic corticosteroids used in ESIs. Corticosteroids are divided into two classes based on particle size and aggregation when compared to a red blood cell (Gegel et al., 2019). Particulate steroids are larger than red blood cells and have longer therapeutic effects due to the slow, continuous release of the steroid from the injection site over time (Gegel et al., 2019; Makkar, Singh, Jain & Goudra, 2016). They are water-insoluble, microcrystalline suspensions (Gegel et al., 2019). The three most common particulate steroids, from largest to smallest particle size, include methylprednisolone, triamcinolone, and betamethasone (Gegel et al., 2019). Any particle that is injected arterially in error poses the risk of embolization and subsequent paralysis; this risk is increased as particle size increases (Gegel et al., 2019). Nonparticulate steroids are notably smaller, water soluble particles with limited aggregation that appear as a clear solution (Gegel et al., 2019; Makkar et al., 2016). Dexamethasone is the only nonparticulate steroid with documented use for ESIs (Gegel et al., 2019). Due to their size and solubility these steroids have a shorter duration of action as they clear rapidly from the spinal canal (Makkar et al., 2016).

In a double blind, prospective, randomized trial on 78 subjects suffering from lumbar radiculopathy, Kennedy et al. (2014) found that both particulate and nonparticulate steroids resulted in statistically similar and significant improvements. However, the nonparticulate group required multiple injections while the particulate group did not. The particulate group received triamcinolone while the nonparticulate group received dexamethasone. Only 2.7% of the particulate group required three injections while 17.1% of the nonparticulate group required this number. In both groups

>70% of subjects had ≥50% pain reduction at 6 months follow-up. During the trial "Not for epidural use" was added to one of the steroid's label which prompted the IRB's recommendation to terminate the study. The researchers were unable to effectively reach their goal in studying 48 patients in each group, which they identify as a significant limitation in addition to the small sample size.

Conversely, in a retrospective comparative study on two cohorts of 494 lumbar radiculopathy patients, Bensler, Sutter, Pfirrmann, and Peterson (2018) found significantly higher pain relief among particulate steroids. The particulate group (321 patients) was treated with triamcinolone and the nonparticulate group (173 patients) was treated with dexamethasone. Both groups received injections via the transforaminal approach using CT guidance. Pain levels were evaluated using a numerical rating scale (NRS) as a percentage and Patients' Global Impression of Change (PGIC) scale. PGIC responses considered to be a positive outcome were "improvement", "better", or "much better". These scores were collected at pre procedure (NRS only), post procedure, one day, one week, and one month intervals. At one week, 43.2% of the particulate group reported improvement compared with 27.7% of the nonparticulate group ($p = 0.001$). At one month, 44.3% of the particulate group continued to report improvement versus 33.1% of the nonparticulate group ($p = 0.019$). The researchers did not include a positive outcome for the NRS data, which served as a limit in addition to the short follow up time and lack of pertinent clinical data such as oral medication use (Bensler, Sutter, Pfirrmann, & Peterson, 2018). The study demonstrates significantly greater effect of particulate corticosteroids when compared to non-particulate corticosteroids in providing clinically relevant 'improvement' for patients suffering from lumbar radicular pain.

Epidural Approaches

Current evidence supports the caudal, interlaminar (IL), and transforaminal (TF) approach to lumbar ESIs in the treatment of inflammatory related pain (Benoy & Azari, 2011). In caudal epidural steroid injections (CESI) the epidural space is accessed through the sacral hiatus (Murakibhavi & Khemka, 2011). Interlaminar epidural steroid injections (ILESI) access the posterior epidural space between adjacent spinal laminae through the ligamentum flavum (Gegel et al., 2019). Transforaminal epidural steroid injections (TFESI) are capable of accessing the anterior epidural space through the intervertebral neuroforamen (Gegel et al., 2019). Caudal epidural steroid injections and ILESIs performed without fluoroscopy are 30-40% likely to miss the intended target area (Roy et al., 2011). Roy et al. (2011) also notes that these approaches may deliver an inadequate corticosteroid concentration to the intended tissue even with fluoroscopic guidance.

Transforaminal Epidural Steroid Injections

The transforaminal epidural technique may reduce radicular pain symptoms more effectively when compared to the caudal and interlaminar approaches (Morgan & Mikhail, 2013). A needle is advanced under fluoroscopic guidance into the foramen at the level of the compressed nerve root (Morgan & Mikhail, 2013). Contrast is injected to confirm accurate spread into the epidural space and rule out intravascular involvement. After the optimal position has been established corticosteroid is injected (Morgan & Mikhail, 2013). Injections are most efficacious when administered within two weeks of symptom onset (Morgan & Mikhail, 2013). Pain relief typically lasts up to three months in duration (Morgan & Mikhail).

Unlike CESIs and ILESIs, the targeted delivery of steroids to the exact site of the afflicted spinal nerves as they exit the neuroforamen is unique to TFESIs (Benoy & Azari, 2011). For this reason, TFESIs require lesser steroid dosing to achieve the same therapeutic effect (Roy et al., 2011; Rados, Sakic, Fingler & Kapural, 2011). This is due in part to the fact that CESIs and ILESIs distribute corticosteroid over the entire epidural space thus requiring more volume of corticosteroid (Roy et al., 2011). Roy et al. (2011) conducted a prospective pilot study of 30 patients aimed at investigating the long-term efficacy of TFESIs on lumbosacral radiculopathy related to disc herniation. The primary outcome of the study was pain relief immediately following the procedure and then at 24 hours, one month, six month, and 12-month intervals. Pain relief was measured using the numeric rating scale (NRS), visual analog scale (VAS), and the Roland-Morris questionnaire. The NRS options ranged from 0 (no pain) to 100 (worst pain). The VAS used a 10 cm scale where 0 indicated no pain and 10 indicated the worst pain ever perceived by the patient. The Roland-Morris questionnaire uses several questions to evaluate the impact of back pain on functional activities. Participants were injected with methylprednisolone and 0.5% bupivacaine under fluoroscopy and received ibuprofen for the 3 days following the procedure. The pilot study demonstrated significant success in long term lumbosacral radicular pain management using TFESIs. According to NRS averages immediate pain relief was experienced in 98% of patients, 79% at 24 hours, 60% at one month, 58.4% at six months, and 59% at 12 months. Visual analogue scale averages were 9.2 post procedure, 0.6 at 24 hours, 1.8 at one month, 3.9 at six months, and 4.2 at 12 months. Roland-Morris scores were collected only pre-procedure, at six months, and at one year and were 18/24, 10/24, and 9/24, respectively. Limits of this

study included the small sample size as well as the inclusion of ibuprofen as this could impact the true pain score measured at 24 hours.

In another study, Kraiwattanapong et al. (2014) researched the short- and long-term outcomes of fluoroscopically guided lumbar TFESIs in a prospective cohort study among 38 DS patients. Inclusion criteria consisted of lower back pain, unilateral leg pain radiating below the knee joint, radiographic evidence of DS with one or two levels of neural compression on MRI, and six weeks of failed conservative treatment. Of the 38 participants, 13 were male and 25 were female. One level stenosis was present in 24 patients (73%) and two-level stenosis in nine patients (27%). Patients were divided into groups based on their level of stenosis. Participants with one level of stenosis underwent one TFESI and participants with two levels received two TFESIs at both sites of pathology. Procedures were performed under fluoroscopic guidance with 80 mg of methylprednisolone and 2 mL of 1% lidocaine hydrochloride. On average, patients received 1.9 injections out of a total of three. Pain was evaluated pre-procedure and then at two weeks, six weeks, three months, and 12 months using visual analog scale (VAS), Roland 5-point pain scale, standing tolerance, walking tolerance, and patient satisfaction. By the end of the trial five patients underwent surgical intervention due to intractable pains related to severe neurogenic claudication and weakness of ankle dorsiflexion. The results were analyzed based on the remaining 33 participants. Visual analog scale scores decreased significantly at two weeks, six weeks, three months, and 12 months ($p < 0.001$). Roland 5-point pain scale scores improved at two weeks and six weeks ($p< 0.001$) but were not significant at three months ($p = 0.09$) and 12 months ($p = 0.091$). Standing and walking tolerance improved only at two weeks ($p < 0.001$) but was insignificant at

six weeks, three months, and 12 months ($p > 0.05$). The study demonstrated significant short-term improvement in both pain scales, standing tolerance, and walking tolerance. Long-term pain reduction remained significant but standing and walking tolerance were limited. Degenerative spondylolisthesis patients with one level stenosis had better results overall than those with two level stenosis (Kraiwattanapong et al., 2014).

In a retrospective study on prospectively collected data among 204 patients with spondylolisthesis, Sencan et al. (2017) evaluated the effectiveness of bilateral TFESIs in DS and IS. One hundred seventy-three patients with DS (122 women, 51 men) and 31 patients with IS (17 women, 14 men) were evaluated between 2009 and 2014. Researchers recorded age, comorbidities, smoking status, number of TFESIs, and follow up time. Pain relief was evaluated as a self-reported percentage and duration of relief was evaluated in days. Successful treatment was defined as >80% pain relief after TFESI. Patients successfully treated with TFESIs had significantly better pain relief for longer duration, had longer follow up periods, and were more likely to request additional TFESIs than patients who were not treated. These results were based on patients self-reported pain relief as a percentage and duration of relief. Bilateral TFESIs decreased pain by more than 80% for 4.5 months in 46.9% of IS patients and for 6 months in 66.1% of patients with DS. The lack of information pertaining to the pain scale utilization, as well as class of steroid selected, served as limitations. The small number of IS participants in comparison to DS was also a limit.

Complications

Despite the documented success of these injections, the US Food and Drug Administration (FDA) has not approved corticosteroid solutions for injection into the

epidural space and actively warns that they may cause serious adverse effects or death (Gegel et al., 2019; U. S. Food and Drug Administration, 2014). In light of the FDA's position against the use of corticosteroids for epidural injection, it is important to review the complications associated with this procedure. The severity of complications related to ESIs vary from minor to major. Complications are typically related to the approach of the injection, needle trauma, vasospastic response, ischemia, infection, the drug injected, and/or to the diluent solution (Gegel et al., 2019). Minor complications do not result in permanent damage and typically manifest as pain exacerbation, vasovagal reaction, headache, and inadvertent dural puncture (Gegel et al., 2019). A gap in literature was identified regarding the risk and complications associated with each individual approach while conducting this review. Major complications include permanent disability, spinal cord injury, vision loss, stroke, epidural hematoma, CSF fistulas, air embolism, blindness, paralysis, and death (Gegel et al., 2019; Kennedy et al., 2014). Epstein (2013) identified 12 deaths in 10 states in the year 2012 secondary to ESIs that were confirmed by the Centers for Disease Control and FDA. These deaths, however, were the direct result of contaminated preservative-free methylprednisolone acetate solution compounded at New England Compounding Center (NECC) in Framingham, Massachusetts (Centers for Disease Control and Prevention, 2012). According to the Centers for Disease Control and Prevention (2012), these solutions were also used for injection into peripheral joint spaces. The report identifies 137 cases of directly affected patients and 14,000 potentially exposed. It is important to clarify that the deaths occurred secondary to contaminated solutions and not from the ESI procedure itself. Beyond that less than 6 major complications related to ESIs occur each year (Racoosin et al., 2015). In a perspective

article in the *New England Journal of Medicine,* Racoosin et al. (2015) discovered 90 serious and sometimes fatal neurologic events reported to the FDA Adverse Event Reporting System (FAERS) between 1997 and 2014. These events included paraplegia, quadriplegia, spinal cord infarction, and stroke. This number did not include patients affected by the aforementioned outbreak of contaminated products (Racoosin et al., 2015). Additionally, while serious complications are a potential risk of ESIs, the rate at which they occur is significantly less than that of surgical complications associated with lumbar spinal surgery (Kennedy et al., 2014). Deyo et al. (2010) conducted a retrospective cohort analysis to evaluate trends and complications involved in lumbar surgery. The cohort included 32,152 patients limited to age 66 or older who underwent surgical lumbar manipulation. Spondylolisthesis was present in 5,915 (18.4%) of patients, which the researcher identified as a factor increasing the likelihood of a lumbar fusion procedure. Major complications were reported in approximately 967 (3.1%) patients and wound complications in 386 (1.2%) in the year 2007 alone.

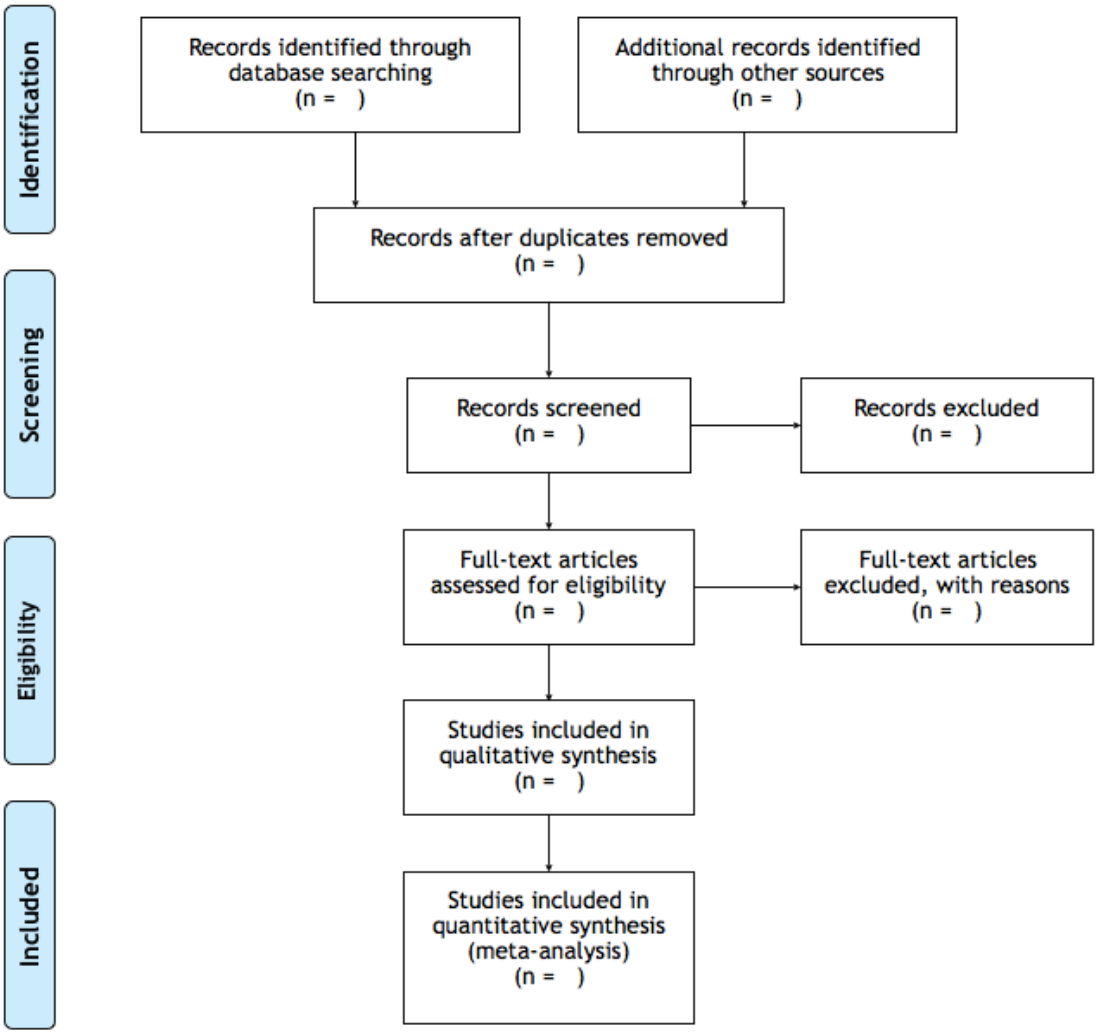
Framework

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) provides specific guidelines for the inclusion of randomized controlled trials in a systematic review (Polit & Beck, 2017). Researchers from multiple, diverse disciplines have relied on PRISMA to prepare transparent, valid reviews for publication (Hutton et al., 2015). For this reason, PRISMA will serve as the framework guiding this study. The PRISMA guidelines include a 27-item checklist (Figure 1) and a four-phase flow diagram (Figure 2) (Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA], 2019). The checklist includes items deemed essential for transparent reporting broken down by title, abstract, introduction, methods, results, discussion, and funding (Liberati et al., 2009). The flow diagram displays the number of identified records, excluded articles, and included studies the researcher found while conducting the review (Liberati et al., 2009).

Figure 1. PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

Figure 2. PRISMA flow diagram



Method

Purpose

The purpose of this review is to determine if TFESIs are effective in managing pain among patients with spondylolisthesis. A systematic review was conducted to determine if TFESIs provide significant radicular pain relief caused by spinal nerve root irritation as seen in symptomatic spondylolisthesis. The research question that guided this systematic review was: are transforaminal epidural steroid injections an effective treatment in the management of chronic lower back pain in patients with spondylolisthesis? The dependent variable under investigation is chronic lower back pain manifested as lumbar radicular pain while the independent variable is treatment with transforaminal epidural steroid injections. This review evaluated all randomized controlled trials, prospective cohort studies, and retrospective case-control studies that met inclusion criteria. Primary outcomes of this review focused on short-term and long-term pain relief. Short-term pain relief was defined as relief lasting less than three months while long-term pain relief was defined as relief lasting greater than three months.

Inclusion/Exclusion Criteria

Inclusion criteria for articles consisted of: minimum patients age of 18, radicular pain consistent with symptomatic spondylolisthesis (spinal stenosis and/or transforaminal stenosis causing nerve root inflammation), treatment with at least one TFESI, identification of a pain scale, and a minimum follow up period of at least two months. Exclusion criteria for articles included: absence of spondylolisthesis among participants, omission of a pain scale, previous lumbosacral surgery, trauma, and infectious processes.

Search Strategy

A detailed search strategy was conducted using CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus, Google Scholar, Medline, and PubMed. Search terms used independently and in combination were: spondylolisthesis, epidural steroid injection, epidural, nerve block, corticosteroids, transforaminal, lumbosacral, radiculopathy, radicular pain, and complications. Reference lists of selected articles were cross-referenced for additional relevant studies. The search was restricted to studies published in English between 2009-2020. The PRISMA flowchart was utilized to select articles for further evaluation.

Data Collection

Data collected from individual articles included: author(s), purpose, study design, year of publication, sample, methods, limitations, steroid and/or local anesthetic injected, number of injections, pain scale, follow up interval, and pain scores following TFESI.

Critical Appraisal

Quality of the individual articles was assessed using Critical Appraisal Skills Programme (CASP) checklists. In the 1980's, the Getting Research Into Practice Project was developed in response to the continued use of interventions that were either contraindicated or not clinically supported by evidence (Critical Appraisal Skills Programme [CASP], 2019). In 1993 this project evolved into CASP. The initial focus of CASP was to raise awareness of the need for evidence in practice (CASP, 2019). The goals have since been refined to highlight the importance of systematic reviews in evidence-based practice, describe characteristics that make up a high-quality review, and provide strategies to locate reviews efficiently (CASP, 2019).

The Critical Appraisal Skills Programme developed checklists to provide researchers with a tool to systematically appraise the quality of a research article. The checklists quickly identify the strengths and weaknesses of a study by evaluating its methodology and reliability (Singh, 2013). These checklists filter out low quality evidence in an effort to strengthen the foundation of individual research designs that builds upon previous studies (Singh, 2013). Checklists are available for the appraisal of randomized controlled trials, systematic reviews, cohort studies, case–control studies, qualitative studies, economic evaluations, diagnostic studies, and clinical prediction rule (CASP, 2019). The CASP Randomized Controlled Trial (Table 1), Cohort Study (Table 2), and Case Control Study (Table 3) Checklists were utilized to critically appraise all articles that met inclusion criteria (CASP, 2019).

Table 1

Critical Appraisal Skills Programme (CASP) Randomized Controlled Trial Checklist

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?			
2. Was the assignment of patients to treatments randomised?			
3. Were all of the patients who entered the trial properly accounted for at its conclusion?			
4. Were patients, health workers and study personnel 'blind' to treatment?			
5. Were the groups similar at the start of the trial?			
6. Aside from the experimental intervention, were the groups treated equally?			
Section B: What are the results?			
7. How large was the treatment effect?			
8. How precise was the estimate of the treatment effect?			
Section C: Will the results help locally?			
9. Can the results be applied to the local population or in your context?			
10. Were all clinically important outcomes considered?			
11. Are the benefits worth the harms and costs?			

Table 2

Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?			
2. Was the cohort recruited in an acceptable way?			
3. Was the exposure accurately measured to minimize bias?			
4. Was the outcome accurately measured to minimize bias?			
5. (a) Have the authors identified all important confounding factors?			
5. (b) Have they taken account of the confounding factors in the design and/or analysis?			
6. (a) Was the follow up of subjects complete enough?			
6. (b) Was the follow up of subjects long enough?			
Section B: What are the results?			
7. What are the results of this study?			
8. How precise are the results?			
9. Do you believe the results?			
Section C: Will the results help locally?			
10. Can the results be applied to the local population?			
11. Do the results of this study fit with other available evidence?			
12. What are the implications of this study for practice?			

Table 3

Critical Appraisal Skills Programme (CASP) Case Control Study Checklist

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?			
2. Did the authors use an appropriate method to answer their question?			
3. Were the cases recruited in an acceptable way?			
4. Were the controls selected in an acceptable way?			
5. Was the exposure accurately measured to minimize bias?			
6. (a) Aside from the experimental intervention, were the groups treated equally?			
6. (b) Have the authors taken account of the potential confounding factors in the design and/or in their analysis?			
Section B: What are the results?			
7. How large was the treatment effect?			
9. Do you believe the results?			
Section C: Will the results help locally?			
10. Can the results be applied to the local population?			
11. Do the results of this study fit with other available evidence?			

Plan for Analysis

Following critical appraisal, data was collected and organized into data collection tables. To individually analyze each study one table evaluated study demographics including study purpose, design, sample, documented cause of lumbar radicular pain (spondylolisthesis, spinal stenosis, and/or foraminal stenosis), and study limitations (Table 4). A second table examined outcomes of the individual studies focusing on the steroid used for injection including dosage, average number of injections, baseline pain scores, duration of follow up, and post-injection pain scores according to the studies respective follow up intervals (Table 5). A third cross study analysis table (Table 6) combined information across all studies to compare significant results. This table compared the steroid, number of injections, duration of follow up, and pain improvement across all studies included in this review.

Table 4

Study Demographics

Citation				
Purpose	Design	Sample	Method	Limitations

Table 5

Study Outcomes

Citation				
Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores

Table 6

Cross Study Analysis

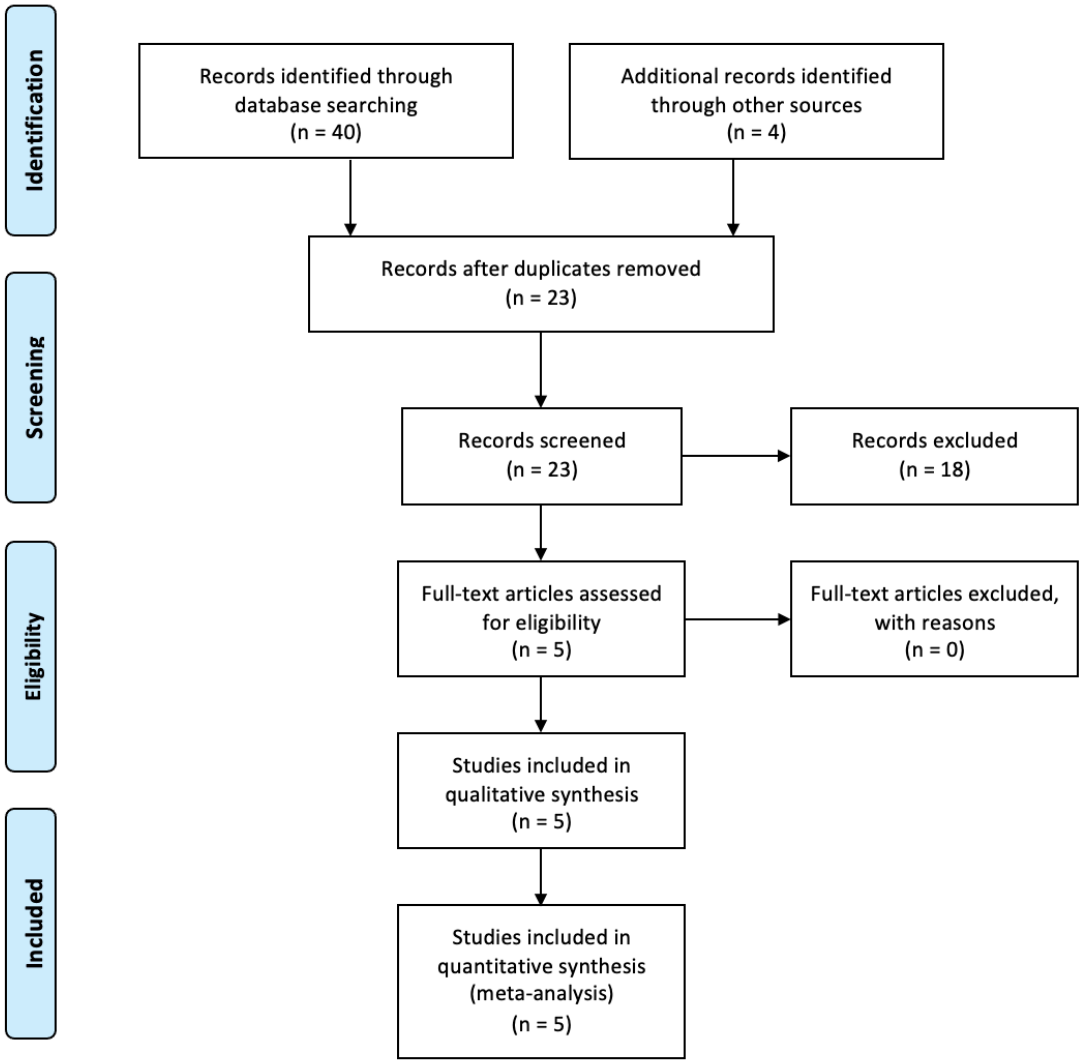
Author & Year	Number of Injections	Overall Outcome	Spondylolisthesis Population	Spondylolisthesis Outcome

Results

An initial database search for “spondylolisthesis” populated 13,911 results. Addition of “steroid” resulted in 182 articles. The results were further narrowed upon inclusion of the term “transforaminal” to 40 studies. Cross-reference analysis of selected articles produced an additional four studies for a total of 44. Next, 21 duplicate articles were eliminated. Upon application of inclusion and exclusion criteria an additional 18 articles were removed. The search process (Figure 3) ultimately yielded five studies for inclusion in this systematic review.

The five selected studies were subsequently critically analyzed. Data extrapolated from the studies were organized into multiple tables according to demographics, outcomes, validity, and cross-sectional analysis. Demographic data obtained focused on: purpose, design, sample, methods, and limitations. Study-specific demographic data tables are highlighted in Table 7. Table 8 provides a synopsis of each study outcomes. Outcome data included steroid type, total number of injections, pain scale, follow up interval, and pain scores. In order to ensure the reliability and ultimately validity of this systematic review, critical appraisals of the five articles using the applicable CASP checklist were then ensued (Appendix, Tables 1-5). Following critical appraisal, one final data table was constructed to provide a cross sectional analysis comparing each study (Table 9).

Figure 3. Completed PRISMA flow diagram



Individual Studies

Vad et al. (2002) evaluated the efficacy of TFESI versus saline trigger-point injections (STPI) on lumbar radiculopathy in a prospective RCT (Table 7). Primary outcome measures included patient satisfaction, pain, and finger-to-floor distance in hip flexion. Inclusion criteria was defined as age older than 18 years, leg pain greater than back pain, symptom duration over six weeks, MRI demonstrating herniated nucleus pulposus (HNP) with 50% intervertebral foraminal narrowing, or symptomatic lumbar radicular pain and sensory or motor defects. Exclusion criteria included prior lumbar surgical intervention, prior ESI, MRI demonstrating large HNP with severe central or foraminal stenosis, progressive neurologic deficits, coagulopathy, allergy to local anesthetic and/or corticosteroids.

Fifty patients were recruited and randomized to a diagnostic group. The TFESI group included 25 patients with a mean age of 41.3 years. Two patients in this group had spondylolisthesis. The STPI group consisted of 25 patients with a mean age of 42 years. Two patients in this group were lost to follow up which left 48 included for final analysis. All injections were performed under fluoroscopic guidance. The TFESI group received 1-3 injections of Betamethasone 9 mg (1.5 mL) and 2% Xylocaine 30mg (1.5 mL). The STPI group received 1-2 injections of normal saline 3 mL. All TFESI and STPI were performed by one proceduralist. Narcotic and/or anti-inflammatory use was prohibited throughout the study. Participants were not blinded to treatment protocol.

Outcomes were measured pre-injection and post-injection at three weeks, six weeks, three months, six months, and twelve months follow up intervals by a nurse blinded to treatment protocol (Table 8). Participants were evaluated using a patient

satisfaction scale, Roland-Morris low back pain questionnaire, finger-to-floor distance in hip flexion, and visual numeric pain scale. The study defined a successful outcome as a patient satisfaction score of 2-3, improvement in Rolland-Morris score by five points, and pain reduction greater than 50% at 12 months follow up.

Vad et al. (2002) found that TFESI had an 84% success rate versus STPI 48% over 1.4 years (P<0.005). The TFESI group experienced maximum symptom improvement at six weeks. Satisfaction score increased from 0.8 ± 0.6 to 2.9 ± 0.7. Roland-Morris scores increased from 8.8 ± 1.2 to 22.1 ± 1. Finger-to-floor distance decreased from 69.6 ± 2.7 cm to 20.3 ± 1.8 cm. Visual numeric pain decreased from 8.8 ± 1.4 to 1.6 ± 0.8. All findings were statistically significant (P< 0.05 each). The STPI group experienced maximum symptom improvement at 12 weeks. Satisfaction score increased from 0.8 ± 0.3 to 1.9 ± 0. Roland-Morris score increased from 9.6 ± 1.3 to 18.3 ± 2.1. Finger-to-floor distance decreased from 64.8 ± 1.4 to 24.4 ± 1.6. 7. Visual numeric pain score decreased from 9.4 ± 1.4 to 3.6 ± 1.1. All results were significant (P<0.05). The two spondylolisthesis patients who underwent TFESI had unsuccessful outcomes demonstrated by a 0% success rate. Statistical significance was unable to be determined due to the small sample size. The authors hypothesized HNP superimposed on the level of the spondylolisthesis impedes the natural recovery process. They state this is likely due to an exacerbation of the pre-existing functional and inflammatory defects affecting the disc, bone, and nerve roots infrastructure in the presence of the herniated disc.

Critical appraisal was performed using the CASP Randomized Controlled Trial Checklist (Appendix, Table 1). Vad et al. (2002) clearly addressed the impact on TFESI versus STPI in lumbosacral radiculopathy patients. While patients were randomized to

treatment groups, they were not blinded to the treatment protocol nor were the proceduralists. This was a limitation of the study. Both groups were similar in age and diagnoses. Two participants were lost to follow-up. Results of this study demonstrated improved short- and long-term outcomes among the TFESI treatment group. The findings are generalizable to HNP induced lumbosacral radicular pain pathologies. However, this may not be an efficacious long-term treatment option in the setting of spondylolisthesis. The small spondylolisthesis sample size of two patients, another study limitation, ultimately precludes the validity and generalizability of these finding.

Kraiwattanapong et al. (2014) conducted a prospective cohort study to evaluate the short- and long-term outcomes of TFESI in DS (Table 7). Inclusion criteria was defined as history of low back pain and unilateral radiating pain at least below the knee joint, slide grade 1 DS on radiograph, one- or two-level neural compression on MRI, and failure of conservative therapy for a minimum of six weeks. Exclusion criteria included previous lumbar surgery, pars defects, previous ESI, allergy to contrast media, gross neurological deficits, cauda equina, and/or inflammatory joint disease.

Thirty-eight patients were included. Five participants were lost to surgical intervention while the remaining 33 completed the study. Thirteen were men and 25 were women. Age ranged between 44-81 years. Subjects were divided into two groups based on one- or two-level stenosis. The level most commonly affected was L4-L5 and was present in 69% of patients. Twenty-four participants (73%) were in the single level group received one-level TFESI while nine participants (27%) were included in the two-level group and received two-level TFESI. Methylprednisolone 80 mg (2 mL) and 1% lidocaine 20mg (2 mL) were administered. All injections were performed by one

proceduralist under fluoroscopic guidance. Total injections ranged from 1-3 with a mean of 1.9.

Outcome measures included pain, standing tolerance, walking tolerance, and patient satisfaction (Table 8). Patients were assessed pre-injection and post-injection at two weeks, six weeks, three months, and 12 months. Statistical significance was associated with $p < 0.05$. Pain was evaluated using VAS and Roland 5-point pain scales. Overall VAS scores decreased significantly from 6.06 ± 1.12 to 2.45 ± 0.91 at two weeks, 3.12 ± 0.96 at six weeks, 3.73 ± 1.07 at three months, and 4.06 ± 1.25 at 12 months ($p < 0.001$). Significant reductions in post-injection VAS scores at each follow up interval were also observed in each group ($p < 0.001$). The one level group demonstrated significantly lower VAS scores versus the two-level group ($p = 0.012$). Overall, Roland 5-point pain scale scores demonstrated significant improvement from 2.79 ± 0.82 to 1.52 ± 0.51 at two weeks ($p = 0.09$) and 2.17 ± 0.7 at six weeks ($p < 0.001$). The three-month value (2.33 ± 0.65) and 12 months (2.3 ± 0.77) did not demonstrate significance ($p = 0.091$). The one level group scores at two weeks, six weeks, and 12 months were significantly reduced ($p < 0.001$) while the two-level group score was significantly reduced at two weeks only ($p= 0.001$). Intergroup comparison showed the one level group values were significantly lower than the two-level group values ($p = 0.012$). Standing tolerance across all participants increased significantly from 1.82 ± 0.88 to 2.76 ± 0.66 at two weeks ($p < 0.001$). Values at six weeks (2.12 ± 0.6), three months (1.9 ± 0.61), and 12 months (1.97 ± 0.59) were not significant ($p > 0.05$). The one level group tolerance increased significantly at two weeks ($p < 0.001$). The two-level group tolerance was not statistically significant changed ($p = 0.218$). The one level group demonstrated

significantly larger increases in standing tolerance versus the two-level group ($p < 0.001$). Walking tolerance exhibited a similar pattern with a significant increase from 1.55 ± 0.83 to 2.09 ± 0.77 at two weeks ($p < 0.001$). Values at six weeks (1.7 ± 0.68), three months (1.7 ± 0.61), and 12 months (1.55 ± 0.56) were insignificant ($p > 0.5$). The one level group tolerance increased significantly at two weeks ($p < 0.012$) whereas the two-level group did not exhibit a significant increase at any follow up interval ($p = 0.510$). The one level group walking tolerance was significantly higher than the two-level group ($p < 0.001$). Patient satisfaction peaked at two weeks and demonstrated significant reductions between two weeks and six weeks, three months and 12 months ($p = 0.02$, $p = 0.002$, and $p = 0.005$, respectively). Neither the one level nor two level group demonstrated statistically significant changes in satisfaction post-injection ($p = 0.2072$, $p = 0.023$) with the exception of a significant decrease at 12 months when compared with week two ($p < 0.05$). Neither group exhibited significant differences in satisfaction scores when compared with each other.

Critical appraisal using the CASP checklist confirmed the integrity and validity of the study (Appendix, Table 2). The authors clearly addressed TFESI with a focus on their impact among DS patients. Following IRB approval, the cohort was recruited in an appropriate manner. The study listed several strategies that ensured accurate measurement of exposure and outcomes and minimized bias. Each participant was classified into treatment group based on their individual MRI findings. Data was collected using multiple validated tools in a uniform and consistent manner. Statistical evaluation was performed using the Wilcoxon rank sum test and analysis of variance. The results of the study showed TFESI effectively reduced short- and long-term pain and

improve short term walking and standing tolerance in DS patients. It also demonstrated better outcomes in the single-level group versus the two-level group. The confounding factors are neither identified nor adjusted for which serves as a limitation of the study. For example, concomitant use of additional conservative therapy among participants during the study was not addressed. Large variations exist among gender, age, treatment group size, and number of injections.

Guha & Bhattacharya (2015) completed a single-blind RCT to compare the outcomes of TFESI among patients with collapsed vertebra, disc protrusion due to degenerative disc disease, and grade I spondylolisthesis (Table 7). Inclusion criteria consisted of lower back pain with radiation to one lower extremity, back and leg pain symptom duration between three and twelve months, correlation of clinically determined level of radiculopathy and MRI, failed analgesic and nonpharmacologic therapy trial of at least three months, and ASA I or II status. Exclusion criteria included multilevel degenerative spine disease, unstable spine, spondylolisthesis (> grade 1), arachnoiditis, progressive neurologic deficit, unstable co-morbidities (uncontrolled diabetes, uncontrolled hypertension), patient refusal, and allergy to contrast media, steroids, or local anesthetic.

Sixty patients were selected and successfully completed follow up. Subjects were grouped according to underlying etiology then randomly allocated to group A, B, or C based on a random number table. Group A included 20 vertebral collapse patients, Group B included 20 disc protrusion patients, and Group C included 20 Grade I spondylolisthesis patients. Baseline demographic data among participants were of similar status. In Group A 68% were male and 32% were female with a mean age of 40.5 ± 7.352

years. Average weight was 52.7 ± 5.313 kg. Thirty percent were ASA Class I and 70% ASA Class II. Mean duration of symptoms was 6.8 ± 1.932 months with average duration of treatment received 3.2 ± 0.918 months. In Group B 66% were male and 34% were female with a mean age 39.7 ± 6.929 years. Average weight was 52.5 ± 5.212 kg. Thirty-two percent were ASA Class I and 68% ASA Class II. Mean duration of symptoms was 6.7 ± 1.766 months with average duration of treatment received 3 ± 0.666 months. In Group C 60% were male and 40% were female with mean age 39 ± 8.313 years. Average body weight was 52.4 ± 5.103 kg. Thirty-six percent were ASA Class I and 64% ASA Class II. Mean duration of symptoms was 6.8 ± 1.619 months with duration of treatment received 3.6 ± 0.787 months.

Each participant received bilateral TFESI at the L1/L2 level under fluoroscopic guidance. A mixture of Depo-medrol 20 mg (0.5 mL) and 0.25% bupivacaine 3.75 mg (1.5 mL). The 2 mL solution was administered on both sides for a total volume of 4 mL. Upon discharge patients were prescribed pregabalin/methyl cobalamin tablets to take at night and tramadol/paracetamol tablets to take twice daily. Outcomes were assessed with VAS and ODI at one hour, one month, three months, and six-month follow-up. Evaluation of VAS and ODI scores was done using one-way ANNOVA analysis and Dunnett's multiple comparison test. Successful treatment was defined as VAS score less than 3 and a decrease in ODI greater than 50%.

Significant improvements were observed in Group A and Group B at one, three, and six months follow up (Table 8). Group A VAS decreased from 6.55 at pre injection to 4.25 at one month (2.300; 95% CI, 1.85 to 2.79), 2.7 at three months (3.850; 95% CI, 3.401 to 4.299), and 2.65 at six months (3.900; 95% CI, 3.451 to 4.349). Group B VAS

decreased from 6.5 at pre injection to 5.2 at one month (1.300; 95% CI, 0.7853 to 1.815), 3.0 at three months (3.500; 95% CI, 2.985 to 4.015), and 2.85 at six months (3.650; 95% CI, 3.135 to 4.165). Group C VAS did not demonstrate significant improvement post-injection. Intervals follow up values at pre-injection, one month, three months, and six months and demonstrated little variation (6.5, 6.3, 6.3, 6.2, 6.2, respectively).

A similar pattern emerged among the ODI values. Group A and Group B appeared to benefit the most while Group C remained unaffected. Group A ODI improved from 38 at pre-injection to 28 at one month (10.00; 95% CI, 8.062 to 11.94), 24 at three months (14.00; 95% CI, 12.06 to 15.94), and 25 at six months (13.00; 95% CI, 1 1.06 to 14.94). Group B values also decreased from 36 at pre injection to 25 at one month (11.00; 95% CI, 8.936 to 13.06), 16 at three months (20.00; 95% CI, 17.94 to 22.06), and 17 at six months (19.00; 95% CI, 16.94 to 21.06) Group C demonstrated little benefit as ODI remained approximately the same pre-injection, one, three, and six months follow up (37, 36, 35, 35, respectively).

A critical appraisal of the trial was performed using the CASP checklist (Appendix, Table 3). The impact of TFESI was clearly addressed and with a focus on the potential benefit among chronic radiculopathies. The assignment of participants to treatment group was randomized and all members were accounted for at the study's conclusion. Participant demographic data was collected and compared using one-way ANOVA analysis and Tukey's multiple comparison test. Baseline characteristics among each group demonstrated similarities in age, sex, weight, ASA status, and pain duration and treatment. Each participant received identical care with uniform adherence to the study protocol and follow up. While the authors confirm this is a single-blind study they

do not clarify which participants are blind to the intervention. This lack of clarification proved to be a limitation of the study that affected other areas as well. The number of proceduralist administering the injections is not addressed nor is status on repeat injections among participants. The authors discussed the prescription of oral pain medication following the intervention but did not identify the duration of treatment which could potentially alter results. While a three-month minimum of failed analgesic and nonpharmacologic therapy was a requirement for inclusion for study the authors did not address active treatment plans at the time of the study which could further alter scores. Statistical evaluation of VAS and ODI measurements was performed with one-way ANNOVA analysis and Dunnett's multiple comparison test. The study found TFESI to be effective in improving disability and treating chronic radicular pain caused by vertebral collapse and disc protrusion (95% CI established). The TFESI were not efficacious in managing pain the spondylolisthesis group. The authors note TFESI provide significant radicular symptoms relief when directly administered at the level of the nerve root compression. The author stated this was the case with collapsed vertebra and disc protrusion but not in grade I spondylolisthesis.

Sencan et al. (2017) conducted a retrospective cohort study using prospectively collected data to compare the efficacy of TFESI in DS and IS (Table 7). Exclusion criteria included scoliosis, prior spine surgery, and grade 3-4 spondylolisthesis. Patients were evaluated using prospectively collected data obtained from the UCSF spine database. Data collected included age, gender, comorbidities, smoking status, pain relief percentage, duration of relief in days, follow up interval, and total TFESI received.

Two hundred and three participants with spondylolisthesis who had undergone bilateral TFESI were included. Participants were divided into a DS and IS group. The DS group included 171 patients. Fifty-one were men and 120 were women with a mean age of 69.5 ± 10.6 years. Comorbidity score was 1.83 ± 1.89. Average number of injections were 1.88 ± 1.35 with a mean follow up period of 1080.74 ± 813.2 days. The IS group included 32 patients. Fourteen were men and 18 were women, with a mean age of 55.81 ± 17.39 years. Comorbidity score was 0.91 ± 1.56. Average number of injections were 2.03 ± 1.31 and mean follow up period was 822.19 ± 797.73 days. The study did not identify the steroid administered.

Outcome evaluation focused on pain relief percentage and period of relief in overall between groups (Table 8) Successful treatment was defined as pain relief > 80% after TFESI. The study demonstrated that TFESI provided statistically significant pain relief in both DS and IS. When both groups were compared and contrasted it became evident that TFESI were more effective in DS than in IS. The rate of successful treatment in the DS group was 66.1% compared to 46.9% in the IS group ($p = 0.009$). The duration of pain relief in the DS group was 181.29 ± 241.37 compared to 140.07 ± 183.62 days in the IS group ($p = 0.065$). The DS group demonstrated no significant correlation between pain relief percent and age-comorbidity score nor number of injections ($p > 0.005$ each). There was significant weak correlation between pain relief percent and number of pain relief days ($r^2 = 0.192$, $p = 0.006$) and follow up period ($r^2 = 0.188$, $p = 0.007$). The IS group demonstrated no significant correlation between pain relief percent and age-comorbidity score ($p > 0.05$). There was significant correlation between pain relief

percent and number of pain relief days ($r^2 = 0.334$, $p = 0.031$), number of injection ($r^2 = 0.250$, $p = 0.002$), and follow up period ($r^2 = 0.247$, $p = 0.002$).

Critical appraisal of Sencan et al. (2017) using the CASP checklist illustrated a clearly focused investigation into TFESI among spondylolisthesis patients (Appendix, Table 4). The cohort was recruited in an acceptable manner while exposure and outcomes were accurately measured and minimized bias risk. The authors identified potential confounding factors to be age, gender, comorbidities, smoking status, total TFESI number, and follow up time. The authors used means and standard deviations for reporting continuous data while inter-group comparisons were made using t-tests for independent variables and Chi-square tests for proportions. Linear regression was also used to assess correlation between pain relief percentile and age-comorbidity score, pain relief days, injection number, and follow up period. The results of the study demonstrated effective pain reduction among both DS and IS following TFESI. Further comparison between groups demonstrated that the DS population experienced greater pain relief for a longer duration when compared to IS. The following limitations were identified while analyzing the article: no specific steroid was identified, older age among DS, increased number of comorbidities among DS, and smaller sample size in IS.

Munjuong & Kummerddee (2020) compared single TFESI and TFESI in addition to CESI using a prospective, single center, randomized, double-blind, controlled trial (Table 7). The purpose of the study was to evaluate the efficacy of each technique on pain and disability among chronic lumbar radiculopathy patients. Inclusion criteria consisted of age between 18 and 80 years, history of chronic lumbosacral radicular pain lasting longer than six months, diagnosis confirmation with MRI studies, and

unsatisfactory pain control. Exclusion criteria included significant neurological deficit, cauda equina syndrome, spinal infection, discitis, psychiatric disorder, pregnancy, language barrier, and/or allergy to local anesthetics, triamcinolone, or contrast media.

Fifty-four patients were randomly assigned to the TC group or T group. The TC group underwent TFESI and CESI while the T group received a single TFESI. Demographic and clinical diagnoses were similar among each group. The TC group included 27 participants, 17 were male (63%) and 10 were female (37%). Average age was 56.6 + 15.9 years and average weight was 70.1 + 11.3 kg. Disc herniation was present in seven patients (26%), spinal stenosis in seven (26%), spondylolisthesis in seven (26%), and failed back surgery syndrome in six (22%). The T group began with 27 participants. Two patients did not complete the study which reduced the total number in T group to 25. Sixteen patients were male (64%) and nine were female (36%). Average age was 55.4 + 15.7 years and average weight was 67.5 + 11.5 kg. Disc herniation was present in six patients (24%), spinal stenosis in seven (28%), spondylolisthesis in seven (28%), and failed back surgery syndrome in five (20%).

All injections were performed under fluoroscopic guidance. The TC group received two injections: a 3 mL mixture of triamcinolone 40 mg in 0.08% Levobupivacaine administered via TFESI followed by a 10 mL mixture of triamcinolone 40 mg in 0.025% Levobupivacaine administered via CESI. The T group received one injection: a 3 mL mixture of triamcinolone 40 mg in 0.08% Levobupivacaine administered via TFESI.

Outcome measures included effective response to treatment and improvement in functional ability. Patients were evaluated prior to injection and at one, two, and three

months follow up. Treatment response was assessed using verbal numeric rating scale (VNRS) and functional using ODI. Successful outcomes were defined as a reduction in VNRS of at least 30% and an improvement in ODI of at least 15 points. Statistical significance was established by $p< 0.05$ (Table 9).

Overall VNRS scores were significantly reduced at one, three, and six months ($P < 0.05$). The TC group demonstrated significantly greater reductions at one and three months ($p = 0.009$, $p = 0.044$). The TC group mean baseline VNRS of 69.6 + 15.1 was reduced by 30% or more in 25 patients at one month (92.6%), 23 patients at three months (85.2%), and seven patients at six months (25.9%). The T group: baselines 74.8 + 16.9 VNRS decreased by 30% or more in 20 participants at one month (80%), 13 participants at three months (52%), and seven participants at six months (28%). Treatment effect at three months was significantly greater in the TC group versus the T group ($p = 0.01$).

Overall ODI scores significantly improved from baseline at one, three, and six months ($P < 0.05$). The difference between the TC group and T group was not found to be significant ($p = 0.235$). In the TC group ODI improved by at least 15 points in 21 patients at one month (77.8%), 18 at three months (66.7%), and 10 at six months (37%). The same 15-point increase in the T group was noted in 16 patients at one month (64%), 12 at three months (48%), and seven at six months (28%). While the TC group had better outcomes at each follow up clinical significance was not established ($p = 0.273$, $p = 0.173$, $p = 0.488$).

The 14 total spondylolisthesis patients VNRS and ODI overall scores demonstrated a greater effect in the TC group. The VNRS scores of the TC group showed greater improvements compared with T group at one, three, and six months but the

differences were not considered significant (p = 0.462, p = 0.070, p = 1.00). The TC group 30% reduction in VNRS scores reported in 7/7 at one month, 7/7 at three months, and 2/7 at six months while the T group reported in 5/7 at one month, 3/7 at three months, and 1/7 at six months. The ODI values demonstrated a similar trend as the TC group again reported greater outcomes compared to the T group. Improvements of at least 15 points in the TC group were reported by 6/7 patients at one month, 7/7 at three months, and 2/7 at six months. The same 15-point change in the T group was present in 4/7 patients at one month, 4/7 at three months, and 2/7 at six months. Again, these values were not statistically significant (p = 0.237, p = 0.051, p = 1.000).

Critical appraisal with the CASP checklist was performed to assess the integrity and validity of the article (Appendix, Table 5). A clearly focused issue was presented, and randomization was confirmed. Participants were randomized to each group however two members of the T group did not complete the trial. Patients were similar and treated equally throughout the study. Participants and follow up assessment personnel were blinded to treatment group. The study concluded that combined TFESI and CESI are more effective than TEFSI alone in improving pain relief. While TC group values were consistently greater than the T group statistical significance was only established at three months (p = 0.010). Spondylolisthesis pain scores demonstrated greater overall improvement in the TC group however the differences were clinically insignificant at each follow up (p = 0.462, p = 0.070, p = 1.000). This is largely due to the small sample size of 14 participants which was a limitation of the study. Other limitations included a lack of assessment into the duration of patient's symptoms as well as any other active pain management interventions by the participants

Table 7
Study Demographics

Vad, V., Bhat, A., Lutz, G., & Cammisa, F. (2002). Transforaminal epidural steroid injections in lumbosacral radiculopathy: a prospective randomized study. *SPINE, 27*(1), 11-16. doi: 10.1097/00007632-200201010-00005

Purpose	Design	Sample	Method	Limitations
To compare TFESI with STPI in the treatment of lumbar radiculopathy secondary to herniated nucleus pulposus	Prospective, randomized controlled trial	48 total patients TFESI: 25 patients 2 Spondylolisthesis Mean age 41.3 years STPI: 23 patients Mean age 42.1 years	Subjects divided into TFESI and STPI group randomized by patient choice. Outcome evaluations performed prior to treatment and at 3 weeks, 6 weeks, 3 months, 6 months, and 12 months by nurse blinded to treatment protocol. Following data collection statistical analysis was performed and results interpreted.	Small sample size Subjects not blinded to treatment Small portion of spondylolisthesis patients

Kraiwattanapong, C., Wechmongkolgorn, S., Chatriyanuyok, B., Woratanarat, P., Udomsubpayakul, U., Chanplakorn, P., Keorochana, G., & Wajanavisit, W. (2014). Outcomes of fluoroscopically guided lumbar transforaminal epidural steroid injections in degenerative lumbar spondylolisthesis patients. *Asian Spine Journal*, *8*(2), 119–128.

Purpose	Design	Sample	Method	Limitations
To report short- and long-term outcomes of lumbar TFESI in degenerative lumbar spondylolisthesis	Prospective cohort study	38 DS patients that received lumbar TFESI 13 men, 25 women Age 44-81 years	Subjects divided into 2 groups: (1) single level spinal stenosis receiving a single level TFESI and (2) two-level spinal stenosis receiving two level TFESI. Evaluated pre-injection and at 2 weeks, 6 weeks, 3 months and 12 months. Outcome measures included	Small sample size Variability in number of injections among patients Pain medication use not addressed

			pain, standing tolerance, walking tolerance, and patient satisfaction.	

Guha, R., & Bhattacharya, D. (2015). Effect of transforaminal epidural block for relief of chronic low back pain with radiculopathy of multiple etiologies. *Indian Journal of Pain*, *29*(3), 155-161.

Purpose	Design	Sample	Method	Limitations
To compare TFESI outcomes among patients with collapsed vertebra, disc protrusion due to degenerative disc disease, and grade I spondylolisthesis.	Randomized, single-blind, controlled study	60 Participants 20 vertebral collapse 20 disc protrusion 20 Spondylolisthesis	Subjects grouped according to MRI etiology. Randomly allocated to group A, B, or C based on a random number table. Outcomes included short- and long-term pain and disability. VAS and ODI scores were assessed pre and post injection at 1, 3, and 6 months (additional VAS at 1 hour postop)	Postop prescription duration unknown. Consistency of proceduralist not addressed. Total injection number unclear

Sencan, S., Ozcan-Eksi, E. E., Cil, H., Tay, B., Berven, S., Burch, S., Deviren, V., & Demir-Deviren, S. (2017). The effect of transforaminal epidural steroid injections in patients with spondylolisthesis. *Journal of Back & Musculoskeletal Rehabilitation*, *30*(4), 841–846.

Purpose	Design	Sample	Method	Limitations
To compare the efficacy of bilateral TFESI in DS and IS	Retrospective cohort study using prospectively collected data	DS: 171 patients 51 men, 120 women Mean age 69.5 years IS: 32 patients 14 men, 18 women Mean age 55.8 years	DS and IS patients that underwent TFESIs were evaluated using data from a prospectively collected spine database. Pain relief, duration of relief, follow up interval, and number of TFESI were recorded. Mean pain relief percentage and duration in days for each patient were calculated and used for statistical analysis.	DS group older, more comorbidities IS group had fewer subjects Lack of age matching within groups

Munjupong, S. & Kumnerddee, W. (2020). Effect of supraneural transforaminal epidural steroid injection combined with caudal epidural steroid injection with catheter in chronic radicular pain management: double blinded randomized controlled trial. *F1000Research, 9*(634), 1-19.

Purpose	Design	Sample	Method	Limitations
To compare the efficacy of CESI plus TFESI versus TFESI alone on pain relief among chronic lumbosacral radiculopathy	Prospective, single center, randomized, double-blind controlled trial	54 patients TC group: 27 T group: 25 Spondylolisthesis: 14	All participants blinded. Patients randomly assigned to group: TC (TFESI+CESI) or T (TFESI). Outcomes measured: effective response to treatment and improvement in functional ability.	Small subgroup sample sizes Duration of symptoms unknown Current pain medication use unassessed

Note. TFESI-transforaminal epidural steroid injection, STPI-saline trigger-point injection, DS-degenerative spondylolisthesis, VAS-visual analog scale, ODI-Oswetry Disability Index, IS-isthmic spondylolisthesis, CESI-caudal epidural steroid injection

Table 8

Study Outcomes

Vad et al. (2002).

Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores
Betamethasone 9 mg (1.5 mL) 2% Xylocaine 30 mg (1.5 mL)	TFESI: 1-3 Mean 1.7 STPI: 1-2 Mean: 1.6	Satisfaction scale Roland-Morris questionnaire Finger-to-floor distance Numeric scale	Pre-injection 3 weeks 6 weeks 3 months 6 months 12 months Mean: 16 months	Successful outcomes defined as patient satisfaction score of 2-3, Roland-Morris improvement by 5 points, pain reduction > 50% at 12 months follow up. TFESI 84% success rate versus STPI 48% over 1.4 years (P<0.005). TFESI group: Maximal improvement at 6 weeks with delay between the final injection and max improvement of 4 weeks. Roland-Morris score increased from 8.8 ± 1.2 to 22.1 ± 1. Visual numeric pain had decreased from 8.8 ± 1.4 to 1.6 ± 0.8. Finger-to-floor distance had decreased from 69.6 ± 2.7 cm to 20.3 ± 1.8 cm. Satisfaction score increased from 0.8 ± 0.6 to 2.9 ± 0.7 (P< 0.05 for each). Spondylolisthesis: unsuccessful outcome (0%) – statistical significance UTA due to small sample size. TFESI may not treat long term radicular pain but However, a temporary response to TFESI may predict a favorable surgical outcome STPI group: maximal improvement at 12 weeks. Roland-Morris score increased from 9.6 ± 1.3 to 18.3 ± 2.1. Visual numeric pain score decreased from 9.4 ± 1.4 to 3.6 ± 1.1. Finger-to-floor distance decreased from 64.8 ± 1.4 to 24.4 ± 1.6. Satisfaction score increased from 0.8 ± 0.3 to 1.9 ± 0.7 (P<0.05).

Kraiwattanapong et al. (2014).

Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores
Methylprednisolone 80 mg (2mL) 1% Lidocaine 20 mg (2 mL)	1-3 Mean 1.9	VAS Roland 5-point pain scale Standing tolerance Walking tolerance	Pre-injection 2 weeks 6 weeks 3 months 12 months	$p < 0.05$ considered statistically significant. VAS: Significant decreases in scores between pre-injection, 2 weeks, 6 weeks, 3 months and 12 months ($p < 0.001$). Roland 5-point pain scale: significant improvement between pre and post-injection at 2 and 6 weeks ($p < 0.001$) but not at 3 and 12 months ($p = 0.09$ and $p = 0.091$, respectively). Significant differences in standing and walking tolerance, only between pre- and post-injection at 2 weeks ($p < 0.001$). At 6 weeks, 3 months and 12 months, there were no significant improvements in standing tolerance and walking tolerance, ($p > 0.05$).

Guha & Bhattacharya. (2015).

Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores
Depo-medrol 20 mg (0.5mL) 0.25% Bupivacaine 3.75 mg (1.5 mL)	UTA	VAS ODI	Pre-injection 1 hour 3 months 6 months	Successful treatment defined as VAS < 3 and ODI reduction > 50%. VAS: significant improvements in groups A and B at 1, 3, and 6 mos. Group A: increased from 6.55 at pre injection to 4.25 at one month (2.300; 95% CI, 1.85 to 2.79), 2.7 at three months (3.850; 95% CI, 3.401 to 4.299), 2.65 at six months (3.900; 95% CI, 3.451 to 4.349)

				Group B: increased from 6.5 at pre injection to 5.2 at one month (1.300; 95% CI, 0.7853 to 1.815), 3.0 at three months (3.500; 95% CI, 2.985 to 4.015), 2.85 at six months (3.650; 95% CI, 3.135 to 4.165) Group C: no significant improvement. Scores of 6.5, 6.3, 6.2, and 6.2, at respective follow ups. ODI: significant improvement in group A and B at 1, 3, and 6 mos. Group A: decreased from 38 at pre-injection to 28 at 1 month (10.00; 95% CI, 8.062 to 11.94), 24 at 3 months (14.00; 95% CI, 12.06 to 15.94), 25 at 6 months (13.00; 95% CI, 1 1.06 to 14.94) Group B: Scores decreased from 36 at pre injection to 25 at 1 month (11.00; 95% CI, 8.936 to 13.06), 16 at 3 months (20.00; 95% CI, 17.94 to 22.06), 17 at 6 months (19.00; 95% CI, 16.94 to 21.06) Group C: no significant improvements; respective scores were 37, 36, 35, and 35

Sencan et al. (2017).

Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores
N/A	DS mean 1.88 IS mean 2.03	Self-reported percentage	Variable Mean: 1040 days	Successful treatment defined as pain relief > 80%. DS group: 72.1 ± 27.5 % pain relief relief (p = .009) lasting 136.5 ± 209.4 days (p = 0.16). 88.8 ± 8.14% had pain relief > 80% (P = 0.001) lasting 181.3 ± 241.4 days (P = 0.001).

				IS group: 54.4 ± 34.3% pain relief (p = .009) lasting 82.1 ± 136.1 days (p = 0.16). 87.3 ± 7.9% had pain relief > 80% (P = 0.001) lasting 140.1 ± 183.6 days (P = 0.038).
Munjupong. & Kumnerddee. (2020).				
Steroid/Local	Number of Injections	Pain Scale	Follow Up	Pain Scores
Triamcinolone 40 mg 0.08 - 0.025% Levobupivacaine	TC: 2 T: 1	VNRS ODI	Pre-injection 1 month 3 months 6 months	Successful outcomes: ≥ 30% reduction of VNRS and ODI improvement by ≥ 15 points. Statistical significance was defined as P< 0.05. VNRS: significant decrease in mean values at 1, 3, and 6 months in both groups (P-value <0.05). Greater improvement in pain relief by TC group at 1 and 3 months (p=0.009, p=0.044). TC group baseline 69.6 + 15.1 reduced ≥ 30% in 92.6% at 1 month, 85.2% at 3 months, and 25.9% at 6. T group: baselines 74.8 + 16.9 reduced ≥ 30% in 80% at 1 month, 52% at 3 months, and 28% at 6 months in both groups ODI: mean values significantly improved at 1, 3 and 6 months while different values between groups statistically insignificant (p=0.235). TC group: ≥ 15 points in 77.8% at 1 month, 67% at 3 months, and 37% at 6 months T group: ≥ 15 points in 64% at 1 month, 48% at 3 months, and 28% at 6 months. TC group had better outcomes, but clinical significance not established (p=0.273, p=0.173, p=0.488). Spondylolisthesis: VNRS scores greater in TC group at all intervals but significance was insignificant (p=0.462, p=0.070, p=1.00). ODI scores greater in TC group at each

	interval but clinically insignificance (p=0.237, p=0.051, p=1.000)

Note. VNRS-verbal numeric rating scale

Cross-Study Analysis

Cross-study analysis was performed and compared the injections, overall study outcome, and percentage and treatment outcome of spondylolisthesis patients (Table 9). This systematic review defined successful short-term pain relief as a reduction in pain for a period of less than three months and long-term relief as relief lasting more than three months. Two articles demonstrated TFESI were not effective in the treatment of radicular pain among spondylolisthesis patients. Vad et al. (2002) identified a 0% success rate in the 4% of spondylolisthesis patients included. The authors were unable to determine statistical significance due to the limited sample size. Guha & Bhattacharya (2015) found effective pain relief among vertebral collapse and discogenic patients while the 33% spondylolisthesis participants did not experience any significant improvements in pain.

Three articles found TFESI to be effective in managing spondylolisthesis related radicular pain. Three articles documented short-term relief while only two demonstrated long-term relief. Kraiwattanapong et al. (2014) found significant short term and long-term pain relief among a sample size of 100% spondylolisthesis patients. Short term relief was demonstrated by reduced VAS and Roland pain scale scores at two and six weeks. Long term relief was reflected by reduced VAS scores at three and 12 months. Sencan et al. (2017) only investigated a sample of spondylolisthesis patients and found significant pain improvements in both DS and IS but noted better outcomes in the DS group. Short- and long-term pain relief was demonstrated by the IS group with 72% pain relief lasting up to four months. The DS group exhibited successful short-term relief demonstrated by a 54% reduction in symptoms lasting up to 2.8 months. Munjupong & Kumnerddee (2020) found successful pain relief while investigating a sample size including 14% spondylolisthesis patients. Due to the small sample size statistical significance was not

established however the trend in outcome scores supports this conclusion. Out of seven spondylolisthesis patients who underwent TFESI five reported successful treatment at one month, three at three months, and one at six months.

Table 9

Cross Study Analysis

Author & Year	Injection	Overall Outcome	Spondylolisthesis Population	Spondylolisthesis Outcome
Vad et al. (2002).	TFESI STPI Average: 1.7	Pain improved by 84% for over 1.4 with maximum benefit achieved at 6 weeks.	2 Participants 4% of sample	Unsuccessful outcome (0%. Unable to determine statistical significance due to small sample size.
Kraiwattanapong et al. (2014)	TFESI Average: 1.9	Pain improved significantly.	38 Participants 100% of sample	Effective short term and long-term pain relief. Short-term effect reduced pain and improved standing and walking tolerance. Long term effect reduced pain (VAS only) but limited improvement in standing and walking tolerance.
Guha & Bhattacharya (2015)	TFESI Average: 1	Significant improvements in pain and disability in vertebral collapse and discogenic groups.	20 Participants 33% of sample	TFESI were not significantly effective in improving pain and function.
Sencan et al. (2017).	TFESI DS average: 2.9 IS average: 2.0	Pain improved significantly.	171 Participants 100% of sample	TFESIs are effective in reducing pain. Successful treatment rates, increased percent pain relief and prolonged duration of relief found in DS patients versus IS.
Munjupong & Kumnerddee (2020).	TFESI TFESI+CESI	TFESI+CESI more effective than TFESI with clinical	14 Participants	Pain scores improved in both groups, but greater improvement seen in

		significance established at 3 months.	26% of sample	TFESI+CESI group. Findings were clinically insignificant at each follow up.

Summary and Conclusions

Spondylolisthesis is defined as anterior displacement of one vertebra relative to the vertebra beneath it (Sencan et al., 2017). The resulting mechanical deformities and stenotic changes lead to spinal nerve compression (Kraiwattanapong et al., 2014). Impingement of the nerve results in the release of pro-inflammatory mediators that irritate the dorsal root ganglion (Mendoza-Lattes et al., 2009). Corticosteroids combat inflammation through their inhibition of prostaglandin synthesis, stabilization of cell membranes, improvement of blood flow, reduction in edema, and inhibition of nociceptive c-fiber conduction (Delport et al., 2004; Vad et al., 2002). Transforaminal epidural steroid injections provide the most specific, targeted delivery of corticosteroid to the dorsal root ganglion (Mendoza-Lattes et al., 2009). Administration of the solution also reduces local levels of interleukin-1, tumor necrosis factor, phospholipase-A2, and other inflammatory mediators via washout (Vad et al., 2002).

The purpose of this systematic review was to investigate the efficacy of TFESI in reducing radicular pain in spondylolisthesis patients. A thorough review of the literature was performed with a focus on the pathophysiology of spondylolisthesis, pharmacokinetics of corticosteroids, and epidural steroid injections. The framework that guided this review was provided by the PRISMA guidelines including a 27-item checklist and a four-phase flow diagram. A comprehensive search was conducted using CINAHL (Cumulative Index to Nursing and Allied Health Literature) Plus, Google Scholar, Medline, PubMed, and cross-referencing reference lists of selected studies. Individual study assessment was performed on five articles that met inclusion criteria. Specific data related to study demographics and outcomes were organized into tables. Critical appraisal

of the individual articles was performed using the CASP checklists. A final cross-study analysis table was constructed contrasting the injection technique(s) used, average number of injections, study outcome, percentage of spondylolisthesis patients included, and outcomes of the spondylolisthesis participants. While performing this search a clear gap in the research was identified among spondylolisthesis patients undergoing conservative therapy versus surgical intervention. Ultimately, this underscores the importance of future research into this population.

This review demonstrated the need for further statistically significant research to confirm the efficacy of TFESI in treating spondylolisthesis related radiculopathy. Additional studies with larger spondylolisthesis specific sample sizes and randomization are therefore recommended. Three articles confirmed short term effect but only two were statistically significant. Two articles confirmed long term effects, but the findings were only statistically significant in one study. Two articles included a sample specific to spondylolisthesis while the remaining articles included a portion of patients within the general sample pool. These articles often included a small subgroup sample that precluded statistical analysis. In addition, consistency among injections and pain scale would allow for increased generalizability of study findings. Each study used a different steroid and local anesthetic combination of lidocaine, bupivacaine, or levobupivacaine and betamethasone, methylprednisolone, or triamcinolone. Number of pain scales used as well as type differed between VAS, VNS, VNRS, percentage, and Roland 5-point scale. Concurrent use of pain medication should also be addressed in an effort to reduce the risk for skewing of result.

Recommendations and Implications for Advanced Nursing Practice

In America chronic pain affects 100 million adults and costs up to $635 billion each year (IOM, 2011). Chronic pain dramatically reduces quality of life as well as productivity (IOM, 2011). CRNAs play an integral role in pain management that ultimately could help to reduce costs, hospitalizations, pain medication requirements, and frequency of office visits. They deliver patient focused treatments with a common goal to decrease pain and improve functionality (AANA, 2014). In rural settings CRNAs are often the only pain professionals available and actively allowing access to chronic pain management (AANA, 2012). They provide access to care in remote areas where patients may not have access to care. They provide interventional procedures in hospitals, outpatient offices, and multidisciplinary clinics across the country (AANA, 2012). These services include trigger point injection, peripheral nerve block, sympathetic nerve block, medial or lateral branch block, joint injection, intrathecal injection, epidural steroid injection, nerve ablation techniques, and evaluation and management of implantable systems (AANA, 2014). For these reasons it is imperative that the CRNA remain up to date and consistently provides care grounded in reliable and valid evidence-based research.

Despite some promising findings, this review concluded that further research into TFESI among spondylolisthesis patients is necessary in order to definitively determine the significance of pain relief achieved. This review may still assist or may encourage future research into effective treatment strategies of spondylolisthesis related chronic pain using epidural corticosteroid injections. Several specialties in healthcare in addition to anesthesia could benefit substantially from this research should it yield a definitive result. CRNAs directly contribute to the collaborative team approach in treating chronic pain as

it is within their scope of practice to perform these injections. Subsequent data collection and analysis into the impact of TFESI specifically among spondylolisthesis patients could fill the current gap in research.

Pain management clinicians may be more likely to consider this treatment modality particularly in light of the current opioid epidemic. Team collaboration between all members of the healthcare team could yield data to drive consistency in pain scales, treatment protocols, policy development, and future guidelines in treating this patient population.

In addition to the potential benefits associated with pain reduction, this research may raise awareness to this condition as a whole. Primary care providers may be more apt to consider a diagnosis of spondylolisthesis in patients presenting with lower extremity and lower back pain. In considering any diagnosis, it is always important to be knowledgeable about the most current, effective, and safe treatments.

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Appendix

Table 1

Critical Appraisal Skills Programme (CASP) Randomized Controlled Trial Checklist

Vad et al. (2002).			
Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?	**X**		
2. Was the assignment of patients to treatments randomised?	**X**		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?			**X**
4. Were patients, health workers and study personnel 'blind' to treatment?			**X**
5. Were the groups similar at the start of the trial?	**X**		
6. Aside from the experimental intervention, were the groups treated equally?	**X**		
Section B: What are the results?			
7. How large was the treatment effect?	48 patients with HNP associated lumbosacral radiculopathy. TFESI 84% success rate versus STPI 48% over 1.4 years. 0% success rate in spondylolisthesis participants.		
8. How precise was the estimate of the treatment effect?	TFESI and STPI impact statistically significant (P<0.005); unable to determine significance in spondylolisthesis group		
Section C: Will the results help locally?			
9. Can the results be applied to the local population or in your context?	**X**		
10. Were all clinically important outcomes considered?	**X**		
11. Are the benefits worth the harms and costs?	**X**		

Note. HNP-herniated nucleus pulposus, TFESI-transforaminal epidural steroid injection, STPI-saline trigger point injection

Table 2

Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

Kraiwattanapong et al. (2014).			
Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimize bias?	**X**		
4. Was the outcome accurately measured to minimize bias?	**X**		
5. (a) Have the authors identified all important confounding factors?			**X**
5. (b) Have they taken account of the confounding factors in the design and/or analysis?			**X**
6. (a) Was the follow up of subjects complete enough?	**X**		
6. (b) Was the follow up of subjects long enough?	**X**		
Section B: What are the results?			
7. What are the results of this study?	TFESI effectively reduce short and long-term pain in DS		
8. How precise are the results?	Statistically significant ($p < 0.001$)		
9. Do you believe the results?	**X**		
Section C: Will the results help locally?			
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice?	TFESI are effective treatment modality when conservatively managing radicular pain in DS		

Table 3

Critical Appraisal Skills Programme (CASP) Randomized Controlled Trial Checklist

Guha & Bhattacharya. (2015).

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?	**X**		
2. Was the assignment of patients to treatments randomised?	**X**		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?	**X**		
4. Were patients, health workers and study personnel 'blind' to treatment?		**X**	
5. Were the groups similar at the start of the trial?	**X**		
6. Aside from the experimental intervention, were the groups treated equally?	**X**		

Section B: What are the results?	
7. How large was the treatment effect?	60 patients with chronic lumbar radiculopathy including 20 spondylolisthesis, 20 vertebral collapse, and 20 disc protrusion patients
8. How precise was the estimate of the treatment effect?	Vertebral collapse and disc protrusion groups had significant improvement in pain and disability (95% confidence established). Spondylolisthesis group did not experience improvement in either outcome.

Section C: Will the results help locally?			
9. Can the results be applied to the local population or in your context?	**X**		
10. Were all clinically important outcomes considered?	**X**		
11. Are the benefits worth the harms and costs?	**X**		

Table 4

Critical Appraisal Skills Programme (CASP) Cohort Study Checklist

Sencan et al. (2017).

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?	**X**		
2. Was the cohort recruited in an acceptable way?	**X**		
3. Was the exposure accurately measured to minimize bias?	**X**		
4. Was the outcome accurately measured to minimize bias?	**X**		
5. (a) Have the authors identified all important confounding factors?	**X**		
5. (b) Have they taken account of the confounding factors in the design and/or analysis?	**X**		
6. (a) Was the follow up of subjects complete enough?	**X**		
6. (b) Was the follow up of subjects long enough?	**X**		
Section B: What are the results?			
7. What are the results of this study?	TFESI significantly more effective relief in DS than IS.		
8. How precise are the results?	$p = 0.009$		
9. Do you believe the results?	**X**		
Section C: Will the results help locally?			
10. Can the results be applied to the local population?	**X**		
11. Do the results of this study fit with other available evidence?	**X**		
12. What are the implications of this study for practice?	Bilateral TFESI are effective conservative treatment options for spondylolisthesis.		

Note. TFESI-transforaminal epidural steroid injection, DS-degenerative spondylolisthesis, IS-isthmic spondylolisthesis

Table 5

Critical Appraisal Skills Programme (CASP) Randomized Controlled Trial Checklist

Munjupong, S. & Kumnerddee, W. (2020). Effect of supraneural transforaminal epidural steroid injection combined with caudal epidural steroid injection with catheter in chronic radicular pain management: double blinded randomized controlled trial. *F1000Research, 9*(634), 1-19.

Section A: Are the results of the trial valid?	**Yes**	**Can't Tell**	**No**
1. Did the trial address a clearly focused issue?	**X**		
2. Was the assignment of patients to treatments randomised?	**X**		
3. Were all of the patients who entered the trial properly accounted for at its conclusion?			**X**
4. Were patients, health workers and study personnel 'blind' to treatment?	**X**		
5. Were the groups similar at the start of the trial?	**X**		
6. Aside from the experimental intervention, were the groups treated equally?	**X**		
Section B: What are the results?			
7. How large was the treatment effect?	54 patients receiving TFEFI or TFESI + CESI		
8. How precise was the estimate of the treatment effect?	TFESI+CESI group yielded more effective pain relief however statistical significance only present at three months (p=0.01). Statistical significance was absent in the spondylolisthesis patients.		
Section C: Will the results help locally?			
9. Can the results be applied to the local population or in your context?	**X**		
10. Were all clinically important outcomes considered?	**X**		
11. Are the benefits worth the harms and costs?	**X**		

Note. TFESI-transforaminal epidural steroid injection, CESI-caudal epidural steroid injection