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Review Article

The Effectiveness of Lumbar Transforaminal Injection of Steroids: A Comprehensive Review with Systematic Analysis of the Published Data

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Abstract

Objective. To determine the effectiveness of lumbar transforaminal injection of steroids in the treatment of radicular pain.

Design. Comprehensive review of the literature with systematic analysis of all published data.

Interventions. Four reviewers independently assessed 39 publications on the effectiveness of lumbar transforaminal injection of steroids. Each reviewer determined if a publication provided any valid information on effectiveness. Assessments were compared, and the data of each publication were evaluated in terms of the rigor with which they were produced and the evidence they provided of effectiveness.

Outcome Measures. The primary outcome sought was the success rate for relief of pain. Improvement in secondary outcomes was noted if reported.

Results. For miscellaneous conditions, the available evidence is limited and is neither compelling nor conclusive. For disc herniation, the evidence is sufficiently abundant to show that lumbar transforaminal injection of steroids is not universally effective but, nevertheless, benefits a substantial proportion of patients, and is not a placebo. Success rates are higher in patients with contained herniations that cause only low-grade compression of the nerve.

Conclusion. In a substantial proportion of patients with lumbar radicular pain caused by contained disc herniations, lumbar transforaminal injection of corticosteroids is effective in reducing pain, restoring function, reducing the need for other health care, and avoiding surgery. The evidence supporting this conclusion was revealed by comprehensive review of all published data and found to be much more compelling than it would have been if the literature review had been of the limited scope of a traditional "systematic review" of randomized, controlled trials only.

Key Words. Radicular Pain; Lumbar; Transforaminal; Injection; Steroids

Transforaminal injection of steroids (TFISs) is one of several treatments using injections for lumbar radicular pain. Others include intramuscular injection of steroids, interlaminar epidural injections, and caudal epidural injections.

Three trials have shown that intramuscular steroids are no more effective than intramuscular normal saline [1–3]. So, for this intervention, the evidence expressly shows no attributable effect beyond placebo.

Interlaminar and caudal injections have traditionally been performed "blind," i.e., without radiographic control. Under these conditions, it has been shown that injections often fail to enter the epidural space, or are intravascular, and therefore fail to reach the affected nerve [4–12]. Controlled trials have shown that interlaminar injections [13–15] and caudal injections [16,17] of steroids are not significantly more effective than sham controls for the relief of pain.

These deficiencies prompted the development and promotion of TFIS. The procedure is distinguished by applying the medication directly onto the affected spinal nerve in the intervertebral foramen that lodges the nerve, under radiographic control. The presumptions upon which the procedure was based were: that using radiographic control

would avoid missing the target nerve and that delivering the medication directly onto the affected nerve would maximize the prospective of having a therapeutic effect [18].

Because of these technical differences, TFIS is not equivalent to conventional epidural injections, and so, its outcomes should not be equated to or grouped with those of other procedures. Yet, some systematic reviews have done so [19] and have dismissed epidural injections, in general, as ineffective or lacking evidence.

In the present era, various insurance companies and government agencies have been reviewing their policies for approving injection procedures for spinal pain or are poised to do so. The present study was undertaken to assist these agencies as well as practicing specialists in understanding the appropriate indication, efficacy, and role of TFIS in the management of lumbar radicular pain. As well, the study was undertaken because previous reviews have not served this particular procedure well for a variety of reasons such as incomplete surveys of the literature and unrealistic expectations of the procedure, such as prolonged relief of pain.

For the present review, a modified systematic method was used. As for conventional, systematic reviews, databases were searched to retrieve the literature, but unlike conventional reviews, the search was not limited to randomized, controlled trials. Artificially restricting a review to controlled trials misrepresents the volume of evidence available and can overlook otherwise potentially informative studies. Conversely, samples recruited for controlled trials may not be representative of the patients that practicing physicians see. As in conventional systematic reviews, each article was independently reviewed by each of the present authors. However, articles were not scored and ranked for quality largely because scales for this purpose have not been validated [20] but also in order to avoid complicating the review with technicalities. Instead, the data of each publication were appraised for how well they supported the effectiveness of the procedure in question.

Methods

The literature on TFIS was retrieved by searching the databases PubMed, Medline, Cochrane, EMBASE Drugs and Pharmacology, and Web of Science, using the terms: lumbar, lumbosacral, transforaminal, epidural, steroids, and injection. As well, publications were identified from the bibliographies of retrieved publications. The retrieved publications were sorted into classes: reviews or essays (which did not provide original data) and studies that provided original data. The latter were further grouped into outcome studies (which simply described the outcomes obtained from the use of the intervention), pragmatic studies (in which the outcomes of TFIS were compared with those of some other procedure expected to have a therapeutic effect), and explanatory studies (in which the outcomes of TFIS were compared with an intervention expected not to have a therapeutic effect).

Outcome studies were accepted for the review on the grounds that such studies provide *prima facie* evidence of how effective the intervention appears to be. Such benchmarks serve to calibrate the external validity of controlled trials, for if authors of controlled studies do not encounter outcomes reasonably similar to those reported in outcome studies, they may not have studied the same phenomenon; either the execution of their treatment differed or their target population differed.

Pragmatic studies were accepted because they can provide two lines of information. First, they can show that an intervention is intrinsically effective if it is more effective than a competing treatment. Second, the outcomes encountered for the index intervention alone provide information about how effective the intervention is in the manner of an outcome study.

Explanatory trials were sought because like an outcome study, they provide a measure of how successful the index treatment is, but also, they reveal what the attributable effect of the index intervention is. The attributable effect is the difference in success rates between the index treatment and a sham treatment. It measures the extent to which the index treatment has therapeutic effects beyond nonspecific effects such as those of placebo or regression to the mean. The reciprocal of the attributable effect is the number needed to treat (NNT) [21,22], which amounts to the number of patients that would need to be treated before one patient could be deemed to have benefited because of the specific effects of the intervention. High values of NNT (such as 10 or greater) indicate a poor treatment, for too many patients would need to be treated in order to achieve one legitimate success. Values of NNT of 2 or 3 indicate that a treatment is effective [23].

Each publication was independently appraised by each of the reviewers, led by a sequence of questions:

1. Does the article provide useful information on the effectiveness of TFIS?
2. Is the information valid?
3. If the conclusions of the authors are not valid, can a valid conclusion nevertheless be calculated from the data published (e.g., adjusting success rates for patients lost to follow-up)?
4. What statement can be made, on the basis of this article, concerning the effectiveness of TFIS?

In addressing these questions, the reviewers were concerned with: if the study used an acceptable technique for TFIS; if the sample studied was representative of patients for whom the treatment was indicated; if valid outcome measures were used; and if outcomes were confounded by cointerventions. For controlled trials, the reviewers were more concerned with if the patients were adequately matched and randomized. They were less concerned with how rigorously technicalities were reported, such as the actual method of randomization, and whether or not sample sizes were calculated prospectively.

Each reviewer would provide an appraisal and summary statement, emphasizing any particular virtues of the study and identifying any fatal flaws. The other reviewers would then indicate if their own appraisal was concordant or not. If necessary, the other reviewers would provide an additional or counter appraisal, and so forth, until agreement was reached. Instead of grading studies for lack of quality, any crucial shortcomings were identified in the narrative that was developed for each study.

The reviewers were practicing physicians who performed the procedure in question in their clinical practices. Variously, each held postgraduate qualifications in anesthesiology, pain medicine, or musculoskeletal pain, or combinations thereof.

Results

The literature search yielded 56 publications. Of these, 17 were systematic or other reviews, or essays on the topic [19,24–39], which did not provide any original data or unique insights or analysis not otherwise available from the original literature. Otherwise, there were 22 outcome studies, 11 pragmatic trials, and 6 explanatory trials. Studies in each category were also stratified according to the indication used for treatment: whether the patients had radicular pain due to disc herniation, spinal stenosis, or other causes.

One prospective, randomized study [40] and one retrospective, case–control study [41] did not compare TFIS with a conventional, control treatment, but each compared the outcomes of two different techniques of TFIS. The techniques differed only with respect to whether the injection was delivered in the intervertebral foramen at the same segmental level as the disc herniation or in the foramen below. Both studies found no statistically significant difference between the success rates of the two techniques. In the light of these results, these studies were accepted and used as outcome studies for the purposes of the present study.

A retrospective study [42] compared the effectiveness of steroids injected at either a superior-anterior location or a superior-posterior location within the intervertebral foramen. It found a trend in favor of the superior-anterior location, but follow-up was conducted for only 2–4 weeks. For lack of sufficient follow-up, this study was not accepted as providing evidence of effectiveness.

A prospective, randomized study [43] compared the effectiveness of steroids delivered at high or low locations within the intervertebral foramen. It found no differences in outcomes. However, this study was accepted as an outcome study for the treatment of radicular pain attributed to spinal stenosis.

Two randomized trials compared different steroid preparations delivered by the same technique of transforaminal injection [44,45]. One found no difference in effect between betamethasone and triamcinolone but provided assessment only at 14 days and did not provide any data on the success rate of either injections [44]. For this reason, it was not accepted as providing evidence on the effectiveness of TFIS. The other compared dexamethasone and triamcinolone, and provided success rates for both agents [45]. This study was therefore accepted as an outcome study of TFIS.

Miscellaneous Conditions

In one study, the patients treated had radicular pain and lumbar scoliosis [46], but the cause of the radicular pain was not specified. Although the study claimed successful outcomes, the definition of success was based on reduction of radicular pain by 2 points out of 10. This value is less than the minimal clinically important change for lumbar radicular pain [47]. Therefore, the success rate claimed was neither valid nor informative. This study was not accepted as providing useful evidence on the effectiveness of TFIS.

In another study, patients who had radicular pain after failed back surgery were treated, but the treatment was confounded by the injection of hyaluronidase as well as triamcinolone [48]. Therefore, it was not an explicit test of TFIS. However, if it is assumed that hyaluronidase is not an active agent, the outcomes reported could be attributed to TFIS. Of the 20 patients, 10 (50% ± 22%) sustained at least 50% relief for 3 months.

In a case report, two patients with epidural lipomatosis were fully relieved of their radicular pain after TFIS using triamcinolone [49]. This might be an encouraging information for a condition that is otherwise difficult to treat, but such a small sample precludes prediction or expectation that the same effect can be expected in other patients.

A retrospective study reported the effectiveness of TFIS in a heterogeneous group of 92 patients with failed back surgery syndrome, spinal stenosis, disc herniation, or unspecified causes of radicular pain [50]. At 12 months after treatment, 38 (41% ± 10%) had at least 50% reduction of pain, but outcome data were not stratified for particular causes of radicular pain.

Spinal Stenosis

The literature, and evidence, on TFIS for radicular pain caused by spinal stenosis was largely limited to outcome studies. There was one pragmatic trial, but no explanatory trials.

Two studies treated only patients with spinal stenosis [51,52] but did not provide informative data on the effectiveness of TFIS. One of these studies [51] treated patients with a caudal injection as well as a TFIS and reported a success rate based on partial relief of pain without defining what “partial relief” meant. The other reported that 64% of patients were completely or somewhat better after TFIS using betamethasone [52] but did not define the meaning of “somewhat better.” It reported that 75% of patients had

an average reduction of pain of 50% [52], which implies that only about 37% of patients had reductions greater than 50%.

One study exclusively treated patients with spinal stenosis [43]. It showed that group scores for pain could be significantly reduced but provided that no data from which success rates or the representative magnitude of relief could be calculated.

Four studies treated patients with various causes of pain but provided separate data on the outcomes of patients with spinal stenosis [40,41,53,54]. One of these studies provided no useful information because it evaluated outcomes only at 2 weeks [41]. The three other studies were prospective studies of patients with foraminal stenosis, two of which reported, respectively, that at 6 months, 26 (54%) of 48 patients achieved at least 50% reduction in radicular pain [40] and 6 out of 10 patients achieved at least 60% relief [53]. Each study used triamcinolone as the steroid. The fourth study reported that 14 (34%) of 41 patients achieved at least 75% relief of pain, and a further eight (20%) had at least 50% relief at 2 weeks after treatment [54]. The agent used was methylprednisolone. That study claimed that 88% of patients with a good outcome at 2 weeks maintained relief at 12 months, but the study did not provide separate data at 12 months on patients with foraminal stenosis.

The single, pragmatic trial was a retrospective, case–control study that compared the outcomes of patients treated with either TFIS or fluoroscopically guided interlaminar epidural injections of methylprednisolone [55]. Outcomes in the two groups were not significantly different statistically, but only group data for pain were reported. Data were not reported that could be used to calculate a success rate for either treatment. Surgery rates, during the 3 years after treatment, were essentially equal (3/19 and 2/19, respectively).

Disc Herniation

There was an abundant literature on the use of TFIS for radicular pain caused by disc herniation. It consisted of outcome studies, pragmatic studies, and explanatory studies.

Outcome Studies

The original study of TFIS, using betamethasone, enrolled 30 patients with disc herniations who were on a waiting list for surgery [56]. After being treated with TFIS, 47% obtained complete relief of pain that was maintained for 2 years, and only 20% required surgery.

The surgery-sparing effect of TFIS was corroborated in a subsequent study that reported that 53 (77%) of 69 patients avoided surgery for 12 months after treatment with TFIS [57]. This study, however, did not provide details on relief of pain or other outcomes, and reported only that successful outcomes amounted to "significant improvement" without defining this descriptor.

A small study reported what appeared to be encouraging outcomes [58], but meaningful outcome data could not be extracted. The study reported group scores using the method of the Japanese Orthopaedic Association, from which success rates could not be derived.

One study provided encouraging but incomplete data [54]. It reported that 29 (17%) of 172 patients had at least 75% relief of pain at 2 weeks after TFIS using methylprednisolone, and a further 36 (21%) had at least 50% relief. The study claimed that this relief persisted for 12 months in 88% of these patients but did not provide more explicit data to that effect.

Another study reported a success rate of 60% (41/68) for providing at least 50% reduction of radicular pain after TFIS using triamcinolone [59], but two features of the study call for a reduction of this estimate. There were 23 additional patients who were treated but whose outcomes were not reported, which potentially reduces the success rate to 45%. Although patients were followed for an average of 3.6 months, an unspecified number of patients were followed for as little as 7 days, which threatens to reduce the success rate even further.

Seven other studies provided more reliable estimates of success rates. Two studies followed patients for 6 months after TFIS using triamcinolone, at which time 12 (60%) of 20 patients had at least 60% relief of pain [53], and 118 (62%) of 191 patients had at least 50% relief of pain [40]. The third study, which used betamethasone, reported that at 12 months, 52 (75%) of 69 patients had at least 50% relief of pain, accompanied by restoration of function [60]. The fourth study, which used methylprednisolone, found that 78% of 40 patients had at least 50% relief of pain at 1 month, reducing to 67% at 6 months, and 55% at 12 months [61]. The fifth study reported that 100% of 53 patients treated with triamcinolone had at least 50% relief at 1 month (although no patient had complete relief); only 39% had this degree of relief when dexamethasone was used [45]. The sixth study reported that 18 (45%) of 40 patients had greater than 75% relief of pain at 90 days, and an additional three patients (7.5%) had between 50% and 75% relief [62]. The seventh study reported 20 patients treated prospectively and 21 treated retrospectively with two injections of 125 mg prednisolone [63]. At 1 month after treatment, 60% $\pm$ 20 of the prospective patients and 67% of the retrospective patients had at least 50% relief of pain. The patients followed prospectively maintained their relief for 90 days.

Pragmatic Studies

One study [64] used TFIS as a control treatment in a study of a minimally invasive surgical treatment. It was not accepted as providing evidence of the effectiveness of TFIS because patients were recruited explicitly if they had previously failed to respond to epidural injections and

because outcome data were not reported in a form that allowed calculation of a success rate.

Several studies compared the effectiveness of TFIS with that of fluoroscopically guided caudal [65,66] or interlaminar [65–68] injections of steroids, or conventional, blind, caudal [68], or interlaminar injections [69–71]. Of these, four were not accepted as providing valid data on either the effectiveness of TFIS or its comparative effect.

One study [69] presented data in an irregular manner. It reported the number of patients with 50% relief of pain at various times of follow-up, but different patients had different and irregular numbers of injections, which varied from one to six at these times. The data presented did not allow calculation of either the success rate of a single injection not contaminated by a subsequent injection or the success rate of a series of injections.

A retrospective, case–control study [72] was not accepted because it was not randomized, and patients had multiple cointerventions as part of a conservative care package. As well, it did not provide data from which success rates could be calculated.

A prospective study [70] was not accepted on multiple grounds. Methodologically, patients were randomized but on the basis of physician preference, which compromised the randomization process. As well, all patients received intensive cointerventions for 7 days, as part of an inpatient program of care. Technically, the authors did not describe their procedure adequately. It seems that they used a dated form of TFIS that involved evoking pain by injecting directly into the nerve sheath. Success rates of this version of TFIS were not reported.

Of the accepted studies, two were weak, retrospective, nonrandomized studies [65,67], but three were prospective, randomized trials [66,68,71]. One of the retrospective studies reported that group pain scores were significantly lower, at 15 days after treatment, in 20 patients treated with TFIS than in 20 patients treated with fluoroscopically guided interlaminar injections [67], but no greater evidence of efficacy was provided. The other retrospective study reported that TFIS, using triamcinolone, provided at least 50% relief of pain in 25 (66%) of 38 patients at 2 months after treatment, and although this success rate was significantly greater than that of fluoroscopically guided caudal injections (3/14; 21%), it was not greater than that of fluoroscopically guided interlaminar injections (16/31; 51%) [65].

The first prospective study showed that TFIS, using dexamethasone, achieved significantly better group improvements in pain at 30 days and at 6 months than blind interlaminar injection of steroids [71], but the data provided did not allow success rates to be calculated. Another prospective study compared TFIS and fluoroscopically guided interlaminar injections of methylprednisolone [68]. Using group data, this study found no statistically significant differences between the outcomes of the two treatments, but it did not provide data on success rates of either treatment.

The third, prospective study [66] was well structured but underpowered for the outcomes that it sought to compare. Patients were randomized to treatment with between one and three fluoroscopically guided caudal or interlaminar injections of steroids or TFIS, using triamcinolone, 30 in each group. There was a trend for the proportion of patients with partial relief to be greater for those treated with TFIS, but this was not statistically significant, and "partial relief" was not defined. What was evident from the study is that the proportion of patients with complete relief at 24 weeks after TFIS (0.33 ± 0.16) was significantly greater than that after caudal injections (0.03 ± 0.06) but not after interlaminar injections (0.10 ± 0.11).

Explanatory Studies

Six studies had the structure of explanatory studies [73–78], but critics might argue that not all were strictly explanatory in nature. Three studies [73,76,78] used transforaminal injection of bupivacaine as the comparison treatment, but it is not known if transforaminal bupivacaine is strictly an inactive treatment. Ostensibly, local anesthetic might have only a temporary relieving effect on pain, but long-lasting effects have not been formally excluded. Nevertheless, studies comparing TFIS and transforaminal bupivacaine have the capacity to determine if adding the steroid to a transforaminal injection is significant.

A fourth study used intramuscular saline as the control treatment [75], which should be acceptable as a suitably inactive treatment for radicular pain, but this control treatment was administered in a different manner—as an office procedure—from that of fluoroscopically guided TFIS. As well, patients were randomized according to patient choice. Both of these factors compromise the internal validity of the study and demote it to providing only weak evidence of efficacy of TFIS.

A fifth study used transforaminal normal saline as the control treatment [74]. With respect to pharmacological activity, this served as an appropriate, inactive control, but it does not control for possible irrigation effects of transforaminal injections. Transforaminal injections might work simply because they wash away inflammatory exudates from around the affected nerve.

The sixth study [77] was more incisive and rigorous in this regard. It randomized patients to TFIS or transforaminal bupivacaine, transforaminal normal saline, intramuscular steroids, or intramuscular normal saline, each performed in a fluoroscopy suite with intramuscular injections mimicking transforaminal injections. Operators did not know which procedure was to be performed until the patient was ready, and they did not know which agent was to be used until the needle had been placed, for either a transforaminal or intramuscular injection. Under these conditions, transforaminal bupivacaine controlled for the

addition of steroids to a TFIS, transforaminal normal saline controlled for the possible effects of simply irrigating the affected nerve, intramuscular steroids controlled for systemic effects of steroids, and intramuscular saline served as a credible sham control.

The first explanatory study [73] did not report on relief of pain or other, conventional outcomes. It used avoidance of surgery as the single outcome measure. It showed that TFIS, using betamethasone, spared patients from surgery significantly more often than did transforaminal bupivacaine alone. Only 29% (95% confidence interval [CI] ±17%) of 29 patients required surgery during the 13 months after treatment with TFIS compared with 66% (±18%) of those treated with bupivacaine. Furthermore, the surgery-sparing effect was maintained during a subsequent 5-year follow-up [79].

The weak explanatory study [75] found that 84% (±14%) of 25 patients treated with TFIS, using betamethasone, achieved at least 50% reduction of pain, accompanied by improvements of at least 5 points on the Roland–Morris instrument persisting for 12 months. In comparison, only 48% (±20%) achieved these outcomes after intramuscular injections of normal saline.

A prospective, randomized, and double-blind trial compared the outcomes of TFIS, using methylprednisolone, and transforaminal bupivacaine [76]. The original publication [76] followed patients for 12 weeks and was supplemented by a second study with 1-year follow-up [78]. The original study [76] found that patients improved after either treatment, but no statistically significant differences arose between the treatment groups. This conclusion was based on continuous group data. Categorical outcomes or success rates were not reported. As well, this study treated patients with either disc herniation or foraminal stenosis, but outcomes were not stratified according to pathology. So, it is not evident if the combined outcomes might have been compromised by treating two different types of pathology.

Outcomes were stratified according to pathology in the subsequent study [78], and no significant differences were found between treatment groups or according to pathology. Conclusions were again based on continuous group data. In this study, patients who underwent surgery or a repeat injection before 3 months were excluded from the analysis, as were 16 patients who failed to attend for review at 3 months. Seventeen patients from the bupivacaine-only group were excluded from the 3-month data compared with 9 from the bupivacaine and steroid group, and the study has therefore not provided valid information about the comparison between transforaminal injections of bupivacaine and transforaminal injections of steroid.

Another prospective study also found no differences in outcomes when TFIS, using methylprednisolone, or transforaminal normal saline were used [74]. This study, too, based its conclusions on group data in which there were no statistically significant differences at 3, 6, and 12 months, but categorical outcomes or success rates were not reported and could not be calculated from the data provided. However, these investigators revisited their data and performed a subgroup analysis.

From that analysis [80], several features arose. First, TFIS was not universally successful. It was no more effective than sham treatment in patients with extruded or sequestrated disc herniations, but it was effective in those patients with contained disc herniations. TFIS was significantly more effective than control treatment for reducing leg pain at 2 weeks and 1 month. As well, patients who had active TFIS tended to have fewer sick-days, fewer resorted to surgery, and twice as many had at least 75% reduction in pain (44% ± 20% compared with 21% ± 16%), but for these latter differences, statistical significance did not emerge because of the small sample sizes involved (25 and 24). However, what did emerge is that for those patients with contained herniations, TFIS was significantly cost-effective at 12 months, achieving a cost-reduction of $12,666 per responder.

The sixth randomized, controlled study was designed primarily to test if the effects of TFIS could be attributed to placebo [77]. For that purpose, it evaluated responses at 1 month after treatment, but it also provided subsequent 12-month data. It found that the various control treatments had success rates for providing at least 50% relief of pain that were statistically indistinguishable. Some 15% (8–22%) of patients obtained at least 50% relief after treatment with transforaminal bupivacaine, transforaminal normal saline, intramuscular steroids, or intramuscular saline. The success rate for TFIS was significantly greater at 54% (36–72%). Depending on which treatment is used as the placebo control, the NNT of TFIS is at worst 3 [77]. Furthermore, this study showed that success relief of pain was accompanied by restoration of function and clinically significant reduction—or elimination—of the need for other health care for radicular pain. All patients recruited for the study came from a neurosurgery unit, and all were destined for surgical treatment. Successful relief of pain by TFIS avoided the need for surgery. During the 12 months after treatment, the success rate from the initial treatment deteriorated, but at 12 months, 11% of patients still had at least 50% relief of pain and a further 14% still had complete relief.

Dose

The literature is divided as to which corticosteroid preparation should be used, the optimal dose or the volume injected. Those studies that reported successful outcomes from TFIS used different agents at different doses (Table 1). The volumes injected, however, were more consistent and ranged between 1 and 2 mL. The pattern of reported practice has been to use either a low dose (40, 50 mg) or high dose (80 mg) of triamcinolone [40,41,45,46,51,53,59,65,66,77], or the equivalent dose of methylprednisolone [48,54,55,61,67,72,74] or

Table 1 The frequency of different doses of various corticosteroids used in those studies that reported some degree of successful outcome from transforaminal injection of steroids. The doses have been aligned in columns of equal potency

Corticosteroid	Number of Studies and Dose Used				
Methylprednisolone	3 40 mg			4 80 mg	
Triamcinolone	7 40 mg	1 50 mg		1 80 mg	1 60–100 mg
Betamethasone	3 5.7 mg		2 8.55 mg	2 11.4 mg	
Dexamethasone	1 6 mg	1 7.5 mg			

betamethasone [52,56,60,69,72,73,75]. Few studies have used dexamethasone [45,71].

Number of Injections

Investigators have used different protocols pertaining to the number of injections (treatments) required to achieve an outcome. Some reported using one to two injections [65], one to three injections [72], one to three injections with a mean of 1.7 [75], or up to four [73]. Some used one to three injections only if prior injections had been of benefit [66]. Others specified the numbers of patients who received 1, 2, 3, or 4 injections or more [50,57,60]. These studies, however, did not provide data on success rates. When those studies that did report the proportions of patients who achieved 50% reduction of pain or better are considered, a revealing pattern emerges (Table 2). It is evident that 94% (±2%) of patients achieved a successful outcome after only one treatment. Only 4% of patients required a second injection, and the use of three or four injections was effectively rare.

Predictors

There is a prevailing view in clinical circles that success rates of treatment for pain tend to be better in patients early in their history and worse when symptoms are chronic. Three studies have provided data in this regard with respect to TFIS (Table 3). One found that duration of symptoms was significantly associated with success rate, two others did not, but the combined data show a significant association. However, the association is not strong. Although success rates are slightly less in patients with chronic symptoms, they are not significantly less, statistically. This is reflected by the low likelihood ratios for duration of symptoms as a predictor of response and the overlap of the 95% CIs of the success rates. Thus, although there is a statistically significant association between outcome and duration of symptoms, it is not clinically significant. Whereas 70% of patients with acute pain can expect to benefit, up to 60% of patients with chronic pain can benefit (Table 3).

One study reported that TFIS was effective only in patients with contained disc herniations but not in patients with extruded or sequestered discs [80]. Two other studies provided additional data. They showed that TFIS was significantly more often successful in patients with low grades of nerve compression (Table 4). In those patients, the success rate was effectively 75%. In patients with high-grade compression, the success rate might be no more than a placebo effect.

Complications

Although reported as "complications" by some authors [81,82], headache, postprocedure pain, facial flushing, vasovagal reactions, rash, transient leg weakness, erectile

Table 2 The number of patients and the number of injections administered in those studies that reported successful responses and for which success rates of transforaminal injection of steroids could be calculated

	Number of Injections			
Reference	1	2	3	4
Cyteval et al. [54]	229			
Narozny et al. [53]	25	5		
Choi et al. [59]	21	21	9	1
Tafazal et al. [78]	25			
Lee et al. [41]	33			
Kabatas et al. [61]	40			
Jeong et al. [40]	222			
Yang et al. [58]	68			
Ng et al. [76]	23	5		
Total	686	31	9	1
Proportion	0.94	0.04	0.01	0.00

Table 3 Successful outcome from transforaminal injection of steroids correlated against duration of symptoms. The *P* value pertains to a chi-squared tested of the data. For each data set, the sensitivity (Sens) and specificity (Spec), and positive likelihood ratio (LR) of short duration of symptoms being a predictor of outcomes are shown, as well as the respective success rates in patients with short duration and long duration of symptoms

Reference Study	Duration (months)	Response		*P*	Sens	Spec	LR	Success Rate (%)
		Yes	No					
Jeong et al. [40]	<6	96	38	0.01	0.67	0.51	1.4	72 ± 8
	>6	48	40					55 ± 10
Lee et al. [41]	<6	12	2	0.62	0.44	0.67	1.3	86 ± 18
	<6	15	4					79 ± 18
Ghahreman et al. [77]	<6	28	22	0.52	0.74	0.33	1.1	56 ± 14
	>6	10	11					48 ± 21
Combined	<6	136	62	0.03	0.65	0.47	1.2	69 ± 6
	>6	73	55					57 ± 9

dysfunction, dizziness, increased blood sugar, hypertensive episode, and nausea do not constitute complications of TFIS. They are all transient phenomena that might be encountered with any injection involving corticosteroids. Dural puncture [83], or unintended injection into a vein [84] or into a disc [85–87], is a technical problem that can occur during TFIS, but they do not constitute complications if they do not cause any impairment.

The only clinically significant complication that has been associated with lumbar TFIS is spinal cord infarction. It has been reported in a total of eight cases [88–92]. The prevailing view is that this complication arises when particulate steroids are unintentionally injected into an artery that reinforces the blood supply of the distal spinal cord [93–95]. Depot preparations of methylprednisolone, triamcinolone, and betamethasone form particles or aggregates that are larger than red blood cells [96] and could form emboli in terminal vessels in the spinal cord. There is also evidence from studies of laboratory animals that steroid preparations may contain ingredients that have a direct neurotoxic effect [97].

Several measures can be adopted to reduce the risk of this complication. Foremost among them is to perform an injection of an adequate volume of contrast medium under continuous, anteroposterior, fluoroscopic imaging, sufficient to ensure that no intraspinal vascular uptake is present. The fluoroscopic field of view should include the spinal canal proximal to the level of injection such that intraspinal arterial uptake may be detected [90–96,98]. Other measures include: digital subtraction imaging, the use of low-volume extension tubing to minimize needle movement between the injection of contrast medium and the injection of steroids, and administering a test injection of local anesthetic before injecting any steroid [92,99].

Some have considered using soluble steroids, such as dexamethasone, in order to avoid particulate steroids [92,96], but it is conspicuous that virtually all of the outcome studies and controlled studies of lumbar TFIS used particulate steroids, only one used dexamethasone [71], and another study found that dexamethasone was less often effective for the relief of pain than was triamcinolone [45].

Table 4 The correlation between response to transforaminal injection of steroids and the grade of nerve compression

Reference Study	Grade	Response		Sens	Spec	LR	Success Rate (%)
		Yes	No				
Choi et al. [59]	Low	44	13	0.86	0.52	1.8	77 ± 11
	High	7	14				33 ± 20
Ghahreman et al. [100]	Low	30	10	0.79	0.70	2.6	75 ± 13
	High	8	23				26 ± 15

LR = likelihood ratio; Sens = sensitivity; Spec = specificity.

Discussion

Although there is an extensive literature on TFIS, many articles do not provide useful and compelling information on effectiveness. Few provided information on secondary outcomes, such as disability, function, and use of other health care. All considered the relief of pain, but many did so incompletely. Some claimed success rates based on improvements that are less than the minimal clinically important change for lumbar radicular pain. Others reported patients achieving at least 50% relief of pain, but did not report baseline scores, or the raw data upon which percentage changes were calculated. Under these conditions, readers cannot tell if the patients treated were typical of ones that readers might treat or perhaps had pain of lesser severity. Despite these deficiencies, there are sufficient other articles that do answer critical questions.

For miscellaneous conditions, such as epidural lipomatosis or failed back surgery syndrome, the literature on TFIS is sorely limited. Although authors have described the use of TFIS for these conditions, the evidence is not compelling for lack of corroborating studies and for lack of any form of controlled study.

Somewhat better is the literature on TFIS for radicular pain attributed to spinal stenosis. According to outcome studies, some 50% of patients achieve 50% relief of pain for 6 months or more, but rigorous studies are lacking and no controlled studies have corroborated this outcome. Without explanatory studies, physicians and consumers alike cannot know if the success rates claimed by outcome studies can be attributed to more than a placebo effect.

It is for radicular pain attributed to disc herniation that the literature is both most abundant and of higher quality. It paints a fairly consistent picture of the effectiveness of TFIS (Figure 1), although outcome studies tended to report more generous success rates than did pragmatic and explanatory studies. TFIS is neither universally successful nor completely successful. About 60% of patients seem to achieve at least 50% relief of pain at between 1 and 2 months, but only about 40% maintain this outcome for 12 months. This partial success has a bearing on how data on the efficacy of TFIS should be reported and interpreted.

When only a subgroup of patients benefits from a treatment, its effectiveness may be camouflaged when group data are used to assess or report effectiveness. Statistically, the good responses of those patients who benefit can be balanced by the responses of patients who do not benefit and those who deteriorate, such that the mean or median score of the group shows little or no change. This phenomenon was highlighted by Ghahreman et al. [77] who showed that their own group data belied the beneficial effects enjoyed by 54% of their patients. After treatment, the median scores for the group showed no significant improvement from baseline, but the distribution of pain scores was bimodal; some patients had high scores, and others had very low scores, but no patient

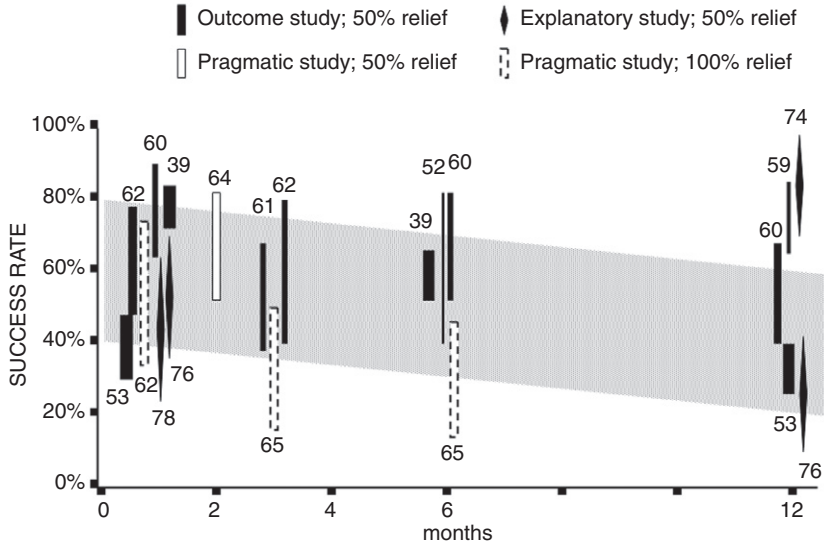

Figure 1 A plot of the success rates for transforaminal injection of steroids, as reported by outcome studies, pragmatic studies, and explanatory studies. The vertical span of the marks represents the 95% confidence intervals of the success rate. The width of the marks is logarithmically proportional to the sample size. The gray zone depicts the trend in deterioration of outcomes over time implied by the largest outcomes studies and the controlled trials. The numbers are the reference numbers of the studies.

had the median score. Using categorical outcomes to determine success rates overcomes this problem of statistical camouflage.

A similar phenomenon was revealed by the studies of Karppinen et al. [74,80]. Although their first study found no differences between active TFIS and sham treatment when group data were used [73], their subsequent subgroup analysis did show that TFIS was significantly effective for patients with contained herniations [80].

With this understanding in mind, it is conspicuous that there have been no studies hostile to the effectiveness or efficacy of TFIS. The only apparently negative studies are those of Ng et al. [76] and Tafazal et al. [78]. They found no differences in outcomes between TFIS and transforaminal bupivacaine, but these studies relied on group data only and did not explore success rates. The authors discussed reasons why the first study [76] did not reproduce the success rates reported by prior outcome studies and considered the possibility that their own study was affected by limiting the number of injections to one. The data in Table 2 argue against this interpretation. Most studies that have reported reasonable success rates treated their patients with only one injection. Other explanations might apply. The study of Ng et al. [76] had a large proportion of patients (17/40) with foraminal stenosis rather than disc herniation. This may have limited the success achieved. As well, group outcomes may have been compromised if there was a large proportion of patients with high-grade compression. TFIS is less often effective in patients with high-grade compressions (Table 4). The study of Tafazal et al. [78] was compromised by exclusion from the analysis of data from patients who required surgery or a repeat injection prior to 3 months and patients who failed to attend a 3-month review.

The evaluation of TFIS can be structured around several null hypotheses, which also constitute the negative arguments that critics or opponents to the treatment might raise in an *ad hoc* manner.

- TFIS does not work.
- TFIS is only a placebo.
- TFIS makes no difference to the burden of illness.
- TFIS is not cost-effective.
- The outcomes of TFIS are not durable.

From a technical, scientific, and philosophical perspective, none of these null hypotheses has been sustained by the published studies. No study has shown them to be true. On the contrary, each has been refuted to greater or lesser extents.

TFIS does work, albeit in a limited proportion of patients. This is evident from the outcome studies, and the pragmatic and explanatory studies. Up to 70% of patients achieve 50% relief of pain at 1 or 2 months after treatment, and about 30% achieve complete relief [66]. TFIS is more often successful in patients with contained disc herniations [78] or patients with low-grade compression [59,100]. It is only marginally less often effective in patients with chronic radicular pain than in patients with acute pain [40,41,100]. TFIS seems to be more often effective than blind, caudal [65,66], or interlaminar [71] injections of steroids. As to whether TFIS is more often effective than fluoroscopically guided interlaminar injections, the evidence to date is mixed with studies being retrospective [64,67], of short duration [67], underpowered [66], or not comparing success rates [68].

TFIS is not a placebo. Statistically, TFIS is more often effective than transforaminal normal saline, intramuscular normal saline, or intramuscular steroids, with a NNT of at worst 3. Whereas two studies found no difference in effectiveness between TFIS and transforaminal bupivacaine [76,78], two other studies that used categorical outcomes showed that TFIS was more often successful than transforaminal bupivacaine [73,77].

TFIS does reduce the burden of illness. This has been shown by the few studies that have reported outcomes other just relief of pain. Successful relief of pain is accompanied by restoration of function [71,75,77] and reduction in the need for other health care for radicular pain [74], and reduces the need for surgery [57,73,77,79].

TFIS is cost-effective. Studies of cost-effectiveness are uncommon or rare in pain medicine. Practicing clinicians who undertake research studies are not accustomed to studying cost-effectiveness; the resources and expertise required are not readily available to them. However, there at least has been one study, which showed that TFIS was, indeed, cost-effective in those patients with contained herniations [80].

The response from a single TFIS is not necessarily enduring. Beyond 1 month, the proportion of patients with continuing relief diminishes. Nevertheless, some 25–40% of patients have relief that lasts 12 months [54,61,77,80]. However, TFIS is not a surgical procedure and should not be judged according to the expectations of a surgical procedure. TFIS does not remove pathology; it is a targeted pharmacological therapy that combats inflammation. It is a treatment that can readily be repeated. There is every prospect that in patients whose pain recurs relief might be reinstated by repeat treatment. However, it is in this regard that the literature is still vacant. There is no published evidence on how frequently TFIS might need to be repeated in order to maintain relief up to and beyond 1 year or indefinitely.

Conclusions

Analysis of all published evidence shows that TFIS is a legitimate treatment for lumbar radicular pain caused by disc herniation or foraminal stenosis. Its effectiveness for pain associated with spinal (central) canal stenosis or other conditions remains speculative. TFIS is not universally successful; it is more likely to relieve radicular pain associated with a contained disc herniation and low-grade nerve compression. The most common definition of a successful outcome is at least 50% reduction of pain

intensity; a patient who does not achieve such an outcome cannot be deemed to have had a successful response. In the overwhelming majority of cases reported in the literature, only one TFIS treatment has been required to achieve a successful outcome. If a patient's pain is relieved but then returns after a time, relief can be reinstated by repeat treatment. A rare but serious complication of TFIS is embolism of a medullary artery resulting in spinal cord infarction. The risk of this complication can be minimized by following prescribed technical guidelines that include specific precautions to avoid intra-arterial injection.

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