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Original Research Articles

The Effectiveness of Repeat Lumbar Transforaminal Epidural Steroid Injections

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Abstract

Objective. The aim of this study was to determine 1) if repeat lumbar transforaminal epidural steroid injections (TFESIs) resulted in recovery of pain relief, which has waned since an index injection, and 2) if cumulative benefit could be achieved by repeat injections within 3 months of the index injection.

Design. Retrospective observational study with statistical modeling of the response to repeat TFESI.

Setting. Academic radiology practice.

Patients. Two thousand eighty-seven single-level TFESIs were performed for radicular pain on 933 subjects. Subjects received repeat TFESIs >2 weeks and <1 year from the index injection.

Methods. Hierarchical linear modeling was performed to evaluate changes in continuous and categorical pain relief outcomes after repeat TFESI. Subgroup analyses were performed on patients with <3 months duration of pain (acute pain), patients receiving repeat injections within 3 months (clustered injections), and in patients with both acute pain and clustered injections.

Results. Repeat TFESIs achieved pain relief in both continuous and categorical outcomes. Relative to the index injection, there was a minimal but statistically significant decrease in pain relief in modeled continuous outcome measures with subsequent injections. Acute pain patients recovered all prior benefit with a statistically significant cumulative benefit. Patients receiving clustered injections achieved statistically significant cumulative benefit, of greater magnitude in acute pain patients.

Conclusion. Repeat TFESI may be performed for recurrence of radicular pain with the expectation of recovery of most or all previously achieved benefit; acute pain patients will likely recover all prior benefit. Repeat TFESIs within 3 months of the index injection can provide cumulative benefit.

Key Words. Repeat; Multiple; Transforaminal; Epidural; Steroid; Injection; Effectiveness; Lumbar

Introduction

Transforaminal epidural steroid injections (TFESIs) are an effective therapy in the treatment of radicular pain; the majority of patients who respond positively require only a single injection [1,2]. Repeat TFESIs are often performed for radicular pain in hopes of cumulative benefit or restoration of benefit that has waned. Little objective data exist to assess either of these potential indications for repeat TFESIs. Currently, there are no evidence-based guidelines addressing the number, frequency, or timing of injections. The purpose of this retrospective study is twofold: 1) to determine if repeat TFESIs lead to restoration of benefit from an index injection that has subsequently diminished; and 2) to determine if repeat TFESIs performed within 3 months of the index injection leads to cumulative pain relief in treatment of single level lumbar radicular pain.

Materials and Methods

Patients

A quality assurance database consisting of 6,582 TFESI procedures performed on 4,161 patients between January 2006 and April 2011 was interrogated. Institutional review board approval was obtained prior to the review and was limited to those patients who had given research authorization. The review was also compliant with the Health Insurance Portability and Accountability Act. All TFESIs were performed for the treatment of radicular pain without or with radiculopathy. Nearly all patient referrals came from physiatrists, neurologists, orthopedic surgeons, and neurosurgeons after clinical assessment and advanced imaging (magnetic resonance imaging, computed tomography [CT], or CT /myelogram). All patients were interviewed prior to the procedure by the interventionalist and pertinent imaging studies were reviewed to ensure appropriateness of the requested injection. If there was a discrepancy between the requested treatment approach and the approach desired by the interventionalist, a consultation with the referring clinician was undertaken and consensus was achieved. The decision to perform a repeat TFESI was made clinically by the referring provider based upon the patient's response to the index injection; either there had been significant benefit from the index injection that had waned or the response to the index injection was positive but incomplete. There were no prescheduled series of injections.

The database was searched for patients who had received repeat single-level TFESI at the L1 through S1 neural foramina greater than 2 weeks and less than 12 months from the index injection. The search returned 2,087 injections performed in 933 patients; the demographics and procedural details of the cohort are presented in Table 1. The neural compressive lesions included disc herniations, synovial cysts, and fixed lateral recess and neuroforaminal narrowing, alone or in combination. Additional subgroups were defined; these were designated acute pain, clustered injections, and acute pain and clustered injections.

The acute pain subgroup was selected based on the observation in a prior study that patients with a shorter duration of pain had a better response to TFESIs [3]. The acute pain subgroup consisted of patients with baseline pain for less than 3 months who received more than one TFESI greater than 2 weeks and less than 12 months from the index injection. The acute pain subgroup search returned 258 patients (576 injections).

The clustered injections subgroup was chosen to evaluate whether early repeat TFESIs performed within 3 months resulted in cumulative benefit. The clustered injections subgroup consisted of patients who had received more than one TFESI greater than 2 weeks and less than 3 months (rather than 12 months) from the index injection. This subgroup likely selects for patients who had a less than optimal initial response. The clustered injections subgroup search returned 496 patients (1,022 injections).

Table 1 Demographic and procedural characteristics of the study cohort (N = 933, N injections = 2,087)

Characteristic	Category	N	% or Mean ± SD
Sex	Female	516	55.3
Age		933	61.2 ± 15.9 years
Index duration of pain	0–3 months	258	27.7
	4–6 months	164	17.6
	7–12 months	113	12.1
	>1 year	398	42.7
Level of injection	L1	3	0.3
	L2	13	1.4
	L3	67	7.2
	L4	165	17.7
	L5	348	37.3
	S1	337	36.1
NRS	Baseline	2087	5.8 ± 2.2
	Week 2	1634	3.6 ± 2.6
	Month 2	1017	3.6 ± 2.7
Number of injections	2	749	80.3
	3	150	16.1
	4	31	3.3
	5	3	0.3

NRS = numerical rating scale of pain, 0–10; SD = standard deviation.

The acute pain and clustered injections subgroup was identified as a corollary to the prior subgroups to assess whether more responsive acute pain patients would achieve more cumulative benefit from early repeat (clustered) injections. The acute pain and clustered injections subgroup consisted of patients who fit the criteria of both the acute pain and clustered injections subgroups; the subgroup search returned 182 patients (375 injections).

Procedure

All interventionalists were board-certified radiologists with fellowship training in either neuroradiology or musculoskeletal radiology. The TFESIs were performed in accordance with the International Spine Intervention Society Guidelines [4]. The vast majority of cases were performed under fluoroscopic guidance (98.9%; 1.1% used CT guidance) using a "safe-triangle" or subpedicular approach. Retroneural or infraneural (triangle of Kambin) approaches were used when anatomic constraints precluded the subpedicular approach and/or suggested other approaches would be more likely to deliver medication to the target nerve at its interface with the compressive lesion. Contrast injections using iodine-based contrast agents (or gadolinium-based contrast agents in patients with iodinated contrast allergies) were performed under live fluoroscopy (or with multislice pulsed CT guidance in

select cases) in anterior–posterior and lateral planes. Digital subtraction imaging was used in select cases where live fluoroscopic visualization was suboptimal. A test dose of 1 cc of preservative free 2% lidocaine (100 mg in 5 cc, APP Pharmaceuticals, LLC, Schaumburg, IL, USA) was used. If there was no central or contralateral neurologic change over the next 1–2 minutes, corticosteroid was injected. Corticosteroids used over the study period included triamcinolone acetonide (Kenalog, 80 mg in 2 cc, Bristol-Myers Squibb, New York, NY, USA), betamethasone sodium phosphate/betamethasone acetate (Celestone, 12 mg in 2 cc, American Regent, Inc., Shirley, NY, USA), and preservative-free dexamethasone sodium phosphate (10 mg in 1 cc, APP Pharmaceuticals, LLC). Betamethasone was the most commonly used agent with triamcinolone being used when betamethasone was not commercially available. Dexamethasone was used exclusively for all transforaminal epidural injections after October 2010 due to growing awareness of the potential for spinal cord infarctions related to particulate corticosteroids.

Clinical Follow-Up

All subject data were entered into an SAS (SAS Institute Inc., Cary, NC, USA) database. Pain relief was measured by a pain numerical rating scale (NRS, 0–10, 0 being no pain and 10 being the worst pain imaginable) measured pre-procedure (baseline) and 2 weeks and 2 months following the injection. The pre-procedure NRS was recorded at the time of the procedure, and the 2-week and 2-month NRS scores were obtained by telephone interview by an independent paramedical assistant. At least three attempts were made to contact each subject at each time point. A successful categorical outcome was defined as ≥50% reduction in NRS compared with baseline or 0/10 pain. Continuous outcomes for pain relief were measured by the mean post-procedure NRS score.

Statistical Analysis

Changes in the response patterns, as measured by the NRS, were estimated using three-level hierarchical linear models (HLMs). HLMs allow data to be grouped, or nested, into higher conceptual levels of data collection. For this study, each patient received repeated injections with functionality assessed at multiple time points for each injection. This data structure introduced clustering into the data that needed to be modeled in order to obtain correct standard errors for the parameter estimates. Specifically, the HLMs for this study were defined with up to three repeated assessments of NRS (denoted as "level 1" in an HLM construct) nested within each injection (level 2). Injections were nested within patient (level 3) (see Appendix I for more details). The models were configured to use the following covariates: time from the injection as a level 1 covariate, injection number as a level 2 covariate, and index baseline pain and chronicity of index pain as patient-level covariates (level 3). The index baseline pain was calculated as the difference of each patient's NRS from the overall mean NRS at index pre-procedure measurement (grand mean centered). The overall change in NRS by subsequent injection number for each model was estimated using a linear effect (0–4). In addition, 2-week and 2-month interaction effects with the subsequent injection term allowed for estimation of changes specific to those follow-up times. Random effects were included in the model to allow the level 1 and 2 intercepts to randomly vary. A two-level HLM was used to test for change in probability of ≥50% reduction in NRS at 2 months with repeat injections. The two-level HLM used only the subsequent injection number as a predictor with similar adjustments for index baseline pain and chronicity of pain. This general modeling strategy was carried forward to look at the changes in response pattern following repeated TFESIs in the subgroup of only those with acute pain, those with clustered injections, and with acute pain managed with clustered injections.

To test if the general shape of the response profiles differed with repeated injections, a likelihood ratio test with three degrees of freedom was constructed to test the joint statistical effect for subsequent injections and this term's interactions with the time post baseline indicator variables. A significant *P* value indicates that the shape of the response profiles over time differed with subsequent injections.

Secondary analysis used generalized estimating equations (GEEs) to test for associations of injection number with proportion of ≥50% reduction in NRS at 2 months and to accommodate multiple procedures within subjects. Injection number was considered a predictor of 50% binary response in models adjusted for index baseline pain and duration of pain (acute 0–3 months vs >3 months).

HLMs were estimated using HLM Software (version 7.0; Scientific Software International, Inc., Skokie, IL, USA). All other statistical analyses were conducted using SAS version 9.3 (SAS Institute). Two-sided *P* values <0.05 were considered statistically significant.

Results

During the study period, 4,161 total patients received TFESIs for unilateral lumbar radicular pain with or without radiculopathy at a single segmental level from L1 through S1. The cohort under study, who received multiple TFESIs, consisted of 933 patients; this constituted 22.4% of the total lumbar TFESI population during the study period.

Entire Cohort

The continuous NRS outcomes for the entire cohort who received repeat TFESIs showed a significant decrease in improvement in NRS with subsequent injections ($P = 0.0311$) (Table 2; Appendix II). The magnitude of the decrease in benefit was, however, very small (Figure 1; Table 2; Appendix II). From the two-level HLM, the probability of ≥50% reduction in NRS at 2 months significantly decreased with subsequent injections (odds ratio

Table 2 Summary of subsequent injection effects in each group overall, at 2 weeks, and at 2 months

Population	Estimated Change in NRS: Baseline to 2 Months			LRT* *P* value	2-Month Benefit Changing?	Direction
	1st Injection	2nd Injection	3rd Injection			
Entire cohort	–2.2	–2.0	–1.7	0.0311	Yes	Decreased benefit
Acute pain	–2.4	–2.7	–2.9	0.0044	Yes	Increased benefit
Clustered	–1.3	–2.3	–3.3	<0.0001	Yes	Increased benefit
Acute and clustered	–1.6	–3.4	–5.2	<0.0001	Yes	Increased benefit

LRT* = likelihood ratio test. This test is a three degree of freedom test for the interaction effects of injection number with the response profile. $P < 0.05$ is suggestive of the hypothesis that the response profiles differed with repeated injections. Estimated changes in NRS are only given for the first three injections since <4% of the sample had four or more injections.
NRS = numerical rating scale.

[OR] = 0.826, *P* value = 0.038) (Appendix II). Patients who received repeat TFESIs were 21% less likely to achieve ≥50% improvement from their index injection baseline pain at 2 months follow-up with subsequent injections. There was thus a minimal but statistically significant decrease in the effectiveness of TFESIs with subsequent injections over this time span (1 year) for the entire cohort.

Acute Pain Subgroup

The continuous data in the acute pain subgroup (baseline pain <3 months) showed a significant increase in benefit with subsequent injections ($P = 0.004$) (Figure 2; Table 2; Appendix II). The acute pain patients recovered all previous benefit, with a statistically significant cumulative benefit.

Clustered Injections Subgroup

The clustered injections subgroup (early repeat TFESIs within 3 months of the index injection) demonstrated a less positive response to the index injection. However, there was a statistically significant overall increase in benefit with subsequent injections ($P < 0.001$) (Figure 3; Table 2; Appendix II). Patients with repeat injections within 3 months did achieve cumulative benefit.

Acute Pain and Clustered Injections Subgroup

The acute pain and clustered injections subgroup (early repeat TFESIs within 3 months of the index injection and baseline pain of <3 months duration) also showed an overall increase in benefit with subsequent injections ($P < 0.001$) (Figure 4; Table 2; Appendix II). The cumulative benefit was greater for acute pain patients with clustered injections than for the entire cohort of clustered injections.

Categorical Outcomes Without Hierarchical Linear Modeling

The categorical outcomes by injection number are seen in Table 3; without hierarchical linear modeling, less data were available to calculate categorical outcomes. It should be noted that this cohort selects for patients with a less than maximal response; the proportion of responders to the index injection is likely less than that for the entire

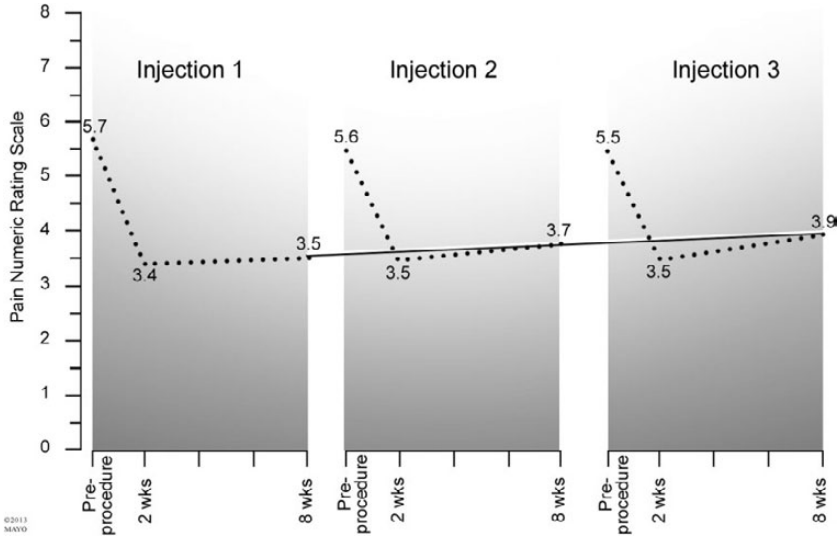

Figure 1 Entire cohort, repeat TFESIs within 12 months. There was a clinically minimal but statistically significant ($P = 0.0311$) decrease in benefit with subsequent injections. TFESI = transforaminal epidural steroid injection.

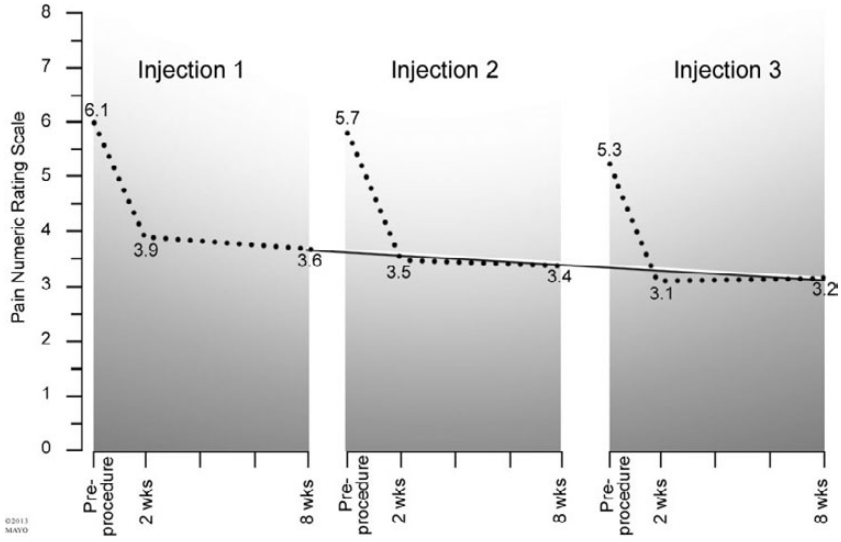

Figure 2 Acute pain subgroup, repeat TFESIs within 12 months in patients with baseline pain <3 months. This subgroup achieved statistically significant ($P = 0.044$) cumulative benefit with subsequent injections. TFESI = transforaminal epidural steroid injection.

lumbar injection population during the study period. For the entire cohort, the proportion of patients achieving ≥50% pain relief (responders) was statistically indistinguishable between an index and a repeat injection, as the confidence intervals overlap. For acute pain patients, the proportion of responders increased on a second injection, but the confidence intervals continue to overlap. When an index injection provided incomplete relief (26% responders), early repeat injection (clustered injections) significantly increased the proportion of responders (45%). The confidence intervals do not overlap between the index and an early repeat injection. This effect was further enhanced in the acute pain patients, where the proportion of responders went from 32% with an index injection to 59% after an early repeat injection within 3 months. The confidence intervals do not overlap. The sample sizes for third injections were too small (confidence intervals too broad) to be meaningful in the clustered and acute and clustered subgroups.

Missing Follow-Up Data

This quality assurance database suffered a number of patients lost to follow-up due to insufficient resources. Outcome data were missing for 453 procedures (21.7%) at 2 weeks follow-up and 1,070 procedures (51.3%) at 2 months follow-up. A GEE analysis of loss to follow-up at 2 months found significant associations of younger age (OR per year: 0.996, 95% confidence interval: [0.995, 0.998]), index pain <3 months (1.106 [1.049,1.165]), increased pre-procedure pain on the NRS (1.030 [1.020, 1.040]), and injection number (0.954 [0.927, 0.982]). The HLM analyses included all available data for patients with

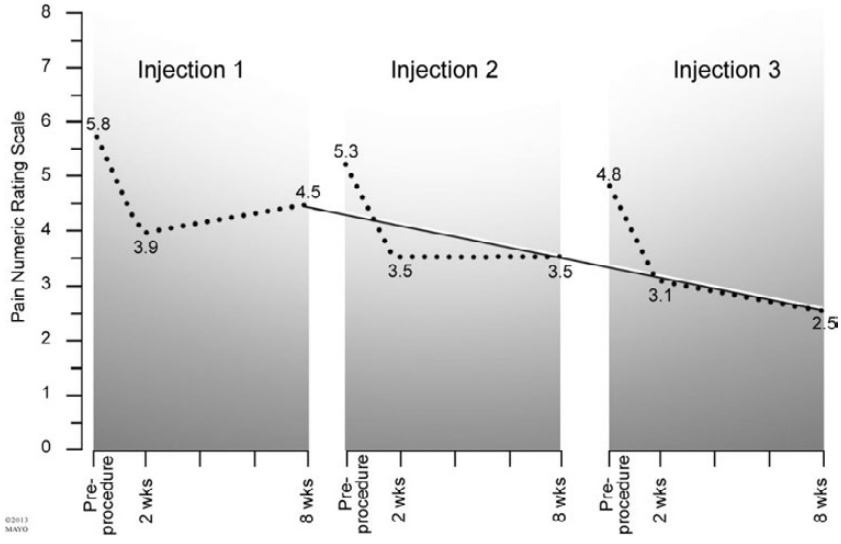

Figure 3 Clustered injections subgroup, repeat TFESIs within 3 months. This subgroup achieved statistically significant ($P < 0.0001$) cumulative benefit with subsequent injections. TFESI = transforaminal epidural steroid injection.

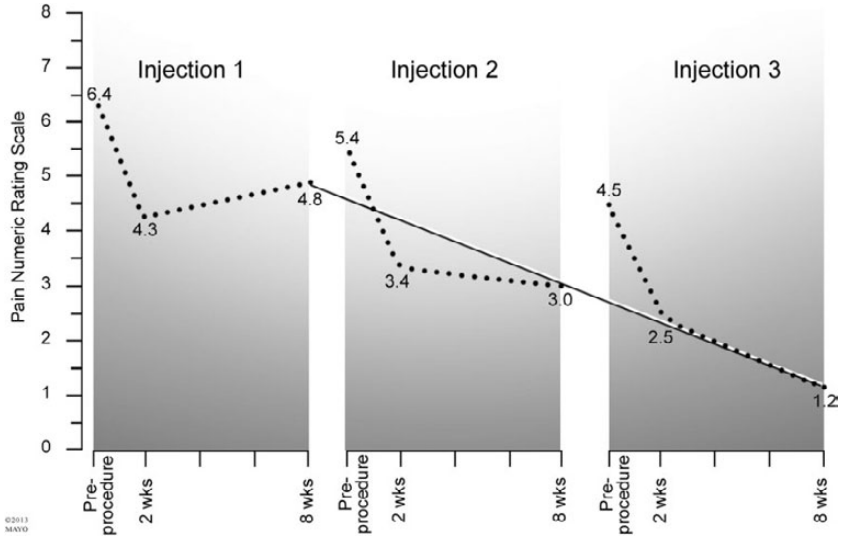

Figure 4 Acute pain and clustered injections subgroup, repeat TFESIs within 3 months with baseline pain <3 months. This subgroup achieved clinically meaningful and statistically significant ($P < 0.0001$) cumulative benefit with subsequent injections. TFESI = transforaminal epidural steroid injection.

complete and incomplete follow-up and still included substantial sample size and distributions.

Discussion

This study demonstrated that in the entire cohort, using modeled continuous outcomes, there was a slight decrease in pain relief at 2 months follow-up with repeat TFESIs, but the magnitude of the change was very small (0.27 NRS, Figure 1). For non-HLM categorical outcomes in the entire cohort, the response rates for first and second injections were indistinguishable. Patients recovered most of the benefit achieved in an initial injection with no cumulative benefit. More responsive acute pain patients (<3 months of pain; Figure 2) recovered all prior benefit with significant cumulative benefit (HLM continuous outcomes) from repeat injections. Patients receiving early repeat (clustered) injections within 3 months had a poorer response to the index injection (Figure 3) but significant cumulative pain relief on subsequent injections. This cumulative pain relief of clustered injections was magnified in both continuous and categorical outcomes in acute pain patients (Figure 4).

Prior to this study, there has been no quantification of the clinical effectiveness of repeat lumbar TFESIs in the management of single-level radicular pain. Furthermore, there are no evidence-based guidelines for the number, frequency, and timing of injections. Historically, Abram recommended repeat epidural steroid injections (up to three) every 1–3 weeks if there was partial improvement in radicular symptoms [5]. This recommendation included blind interlaminar and caudal epidural steroid injections that may not have reached the intended target. A more recent literature review did not identify any studies that could specifically support guidelines for the frequency and timing of epidural steroid injections [6]. There is limited evidence that can help define what constitutes the appropriate partial response to suggest a repeat injection but no evidence to support the practice of a series of injections [6].

The majority of patients who undergo TFESIs for radicular pain require only a single injection; in a comprehensive review of the literature, MacVicar and colleagues identified nine studies with categorical outcomes of ≥50% pain relief [1]. Of the patients who achieved ≥50% pain relief, 94% (±2%) required a single injection and 4% required a second injection to achieve this level of pain relief. MacVicar does not identify the overall proportion of treated patients who underwent multiple injections. In the study by Kennedy and colleagues, in which greater than

Table 3 Categorical outcomes: proportion of patients achieving ≥50% improvement in NRS at 2 months by injection number

Injection	Entire Cohort % (95% CI)	Acute % (95% CI)	Clustered % (95% CI)	Acute and Clustered % (95% CI)
1st	45.1 (40.3, 49.9)	44.2 (33.3, 55.2)	26.4 (17.4,35.4)	32.3 (15.9, 48.7)
2nd	41.9 (37.6, 46.2)	54.7 (46.2, 63.3)	45.0 (39.1, 51.0)	58.7 (48.7, 68.7)
3rd	34.7 (25.1, 44.4)	32.6 (11.3, 53.8)	40.1 (13.0, 67.3)	22.0 (0.0, 69.6)

CI confidence interval; NRS = numerical rating scale.

70% of disc herniation patients achieved ≥50% pain relief at 6 months, 58% underwent a single TFESI, 31% underwent two TFESIs and 10% had three injections in 6 months [2]. During our study period, 22.4% of patients had repeat TFESIs within a year, either in hopes of cumulative relief or recovery of lost benefit. Within 1 year from the index injection, 18% of our patient population had a second TFESI only, and 3.6% a third injection. Repeat injections were thus used with modest frequency, even though our study population was much older (mean age 61 years) than that of the Kennedy study (mean age 36 years [2]), and 43% of our patients had pain for greater than 1 year. The patient characteristics in our study cohort (older age and hence likely a higher proportion of fixed lesions, and a high proportion of chronic pain patients) militate against durable success with single injections, making understanding responsiveness to repeat injections clinically highly relevant.

Patient with radicular pain for <3 months were more responsive to repeat TFESI; there was complete restoration of previous pain relief and a significant cumulative benefit with HLM continuous outcomes. With non-HLM categorical outcomes, there was a 10% increase in response rate for a second injection, although the confidence intervals overlap. This has also been demonstrated in prior studies with single injections. MacVicar and colleagues pooled data from three studies using 6 months as defining acute vs chronic pain; they found that 69% of patients with acute pain can expect benefit compared with 57% with chronic pain [1]. This finding was statistically but not clinically significant. Kaufmann and colleagues noted a statistically and clinically significant difference in the proportion of responders to a single TFESI based on the duration of pain; 62% of patients with pain <3 months achieved >50% reduction in NRS at 2 months vs 38% of patients with pain >12 months [3].

When patients received early repeat TFESIs within 3 months (clustered injections), there was a statistically significant increase in pain relief with subsequent injections. The proportion of responders increased from 26% for the index injection to 45% with a second injection; the confidence intervals do not overlap. There was clear selection for an incomplete response in this subgroup, as was anticipated. Patients who have a positive but incomplete response to an initial TFESI may achieve cumulative benefit when repeat TFESIs are performed early following the first injection. Another study on this cohort has demonstrated that the pain relief and functional recovery response measured at 2 weeks follow-up strongly predicts longer term outcomes; it may be reasonable then to consider a repeat TFESI for those patients with a positive but inadequate response at 2 weeks follow-up [7]. Patients with relatively acute pain (<3 months duration) who underwent repeat TFESI within 3 months experienced a statistically significant increase in benefit; they also achieved a clinically significant cumulative reduction (≥50%) in mean NRS. The model predicted a mean NRS = 4.8 at 2 months follow-up of an initial injection, mean NRS = 3.0 after a second injection, and a mean NRS = 1.2 at 2 months follow-up following a third injection (Figure 4).

There is no prior published evidence to support or direct the use of repeat TFESIs. This study demonstrates that patients with recent onset of pain can anticipate recovery of benefit with repeated TFESI and some cumulative effect. Patients with more chronic pain may see a decrease of benefit with repeated injections. When the response to an index injection is positive but incomplete, early reinjection can yield cumulative benefit; this effect is greater in patients with a shorter duration of pain at the index injection. The decision to perform repeat TFESI remains dependent on the response to the initial injection and the patient's clinical scenario, including features such as the degree of neural compression, which may predict long-term response [8]. This study provides no support for the prescription of an a priori treatment course of multiple injections.

There are several limitations to this study. This is a retrospective interrogation of a quality assurance database, which had a number of patients lost to follow-up. The GEE analysis showed that the lost to follow-up patients were more likely to be of younger age, have pain of <3 months duration, and have higher pre-procedure pain. In prior studies, these factors have all predicted a favorable response to TFESI, suggesting that the response rates to repeat injections may be underestimated [3]. Each subgroup analysis resulted in a smaller sample size that limits the generalizability of the statistical analysis. Sample sizes of subgroups, however, remained adequate for statistical modeling. The 2-month follow-up data is also limited by the study design, which allowed repeat injections to be performed in that time window. Multiple steroid preparations were used over the course of this study without stratification. However, a previous retrospective examination of this study population demonstrated that there was no evidence that a non-particulate steroid was less effective than a particulate steroid in the treatment of lumbar radicular pain [9]. There was no stratification of results by the nature of the compressive lesion (disc, synovial cyst, fixed lateral recess or foraminal stenosis). This is being investigated and will be addressed in a future study. The inclusion of all compressive lesions in this study makes the results broadly applicable to clinical practice.

Conclusion

Most patients do not require repeat TFESIs in treatment for lumbar radicular pain. Repeat lumbar TFESI performed within 1 year of the index procedure in hopes of restoration of benefit may see slightly diminished levels of pain relief at 2 months with subsequent injections. Patients with acute pain syndromes (<3 months) on average will have restoration of prior benefit and a small cumulative benefit from repeat TFESIs performed within a year of the index injection. Patients with an incomplete initial response to TFESIs who receive early repeat TFESIs within 3 months can achieve cumulative benefit. Acute pain patients with

an initial incomplete response who received repeat injections within 3 months demonstrated a greater, clinically significant cumulative benefit. These findings suggest a more aggressive approach in treating acute single segment lumbar radicular pain. An incomplete response at 2 weeks postinjection can reasonably provoke a repeat TFESI. Because there is a paucity of literature regarding repeat TFESIs, further prospective investigation is warranted.

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Appendices

Appendix I

Summary framework of hierarchical linear models

Level	Equation
1 (Time)	$NRS = \pi_{0jk} + \pi_{1jk} \times (\text{Week } 2_{ijk}) + \pi_{2jk} \times (\text{Month } 2_{ijk}) + e_{ijk}$
2 (Injection order)	$\pi_{0jk} = \beta_{00k} + \beta_{01k} \times (\text{Injection}_{jk}) + r_{0jk}$
	$\pi_{1jk} = \beta_{10k} + \beta_{11k} \times (\text{Injection}_{jk})$
	$\pi_{2jk} = \beta_{20k} + \beta_{21k} \times (\text{Injection}_{jk})$
3 (Patient)	$\beta_{00k} = \gamma_{000} + \gamma_{001}(\text{Baseline}_k) + \gamma_{001}(\text{Chronic}_k) + u_{00k}$
	$\beta_{01k} = \gamma_{010}$
	$\beta_{10k} = \gamma_{100}$
	$\beta_{11k} = \gamma_{110}$
	$\beta_{20k} = \gamma_{200}$
	$\beta_{21k} = \gamma_{210}$

$NRS_k = \gamma_{000} + \gamma_{001} \times \text{Baseline}_k + \gamma_{010} \times \text{Injection} + \gamma_{100} \times \text{Week}\ \ 2_{ijk} + \gamma_{110} \times \text{Week}\ \ 2_{ijk} \times \text{Injection}_{jk} + \gamma_{200} \times \text{Month}\ \ 2_{ijk} + \gamma_{210} \times \text{Month}\ 2_{ijk} \times \text{Injection}_{jk} + r_{0jk} + u_{00k} + e_{ijk}$. NRS = numerical rating scale.

Appendix II

Parameter estimates and significance levels for three-level HLM models of NRS outcomes

Sample	Fixed Effects	Coefficient	SE	*P* value
Entire group	Intercept	5.654	0.076	<0.001
N scores = 4,738	Index baseline score	0.502	0.501	<0.001
2,087 baseline	Index chronicity	0.201	0.097	0.036
1,634 2 weeks	Injection	–0.065	0.058	0.264
1,017 2 months	Week 2 intercept	–2.224	0.089	<0.001
N injections = 2,087	Week 2 × injection	0.119	0.088	0.174
N patients = 933	Month 2 intercept	–2.155	0.200	<0.001
	Month 2 × injection	0.268	0.111	0.016
Acute pain	Intercept	6.067	0.079	<0.001
N scores = 1,243	Index baseline score	0.407	0.039	<0.001
576 baseline	Injection	–0.369	0.112	0.001
437 2 weeks	Week 2 intercept	–2.197	0.169	<0.001
230 2 months	Week 2 × injection	–0.004	0.160	0.982
N injections = 576	Month 2 intercept	–2.425	0.264	<0.001
N patients = 258	Month 2 × injection	0.135	0.269	0.616
Clustered injections	Intercept	5.807	0.090	<0.001
N scores = 2,169	Index baseline score	0.525	0.029	<0.001
1,022 baseline	Index chronicity	0.390	0.126	0.002
791 2 weeks	Injection	–0.481	0.098	<0.001
356 2 months	Week 2 intercept	–1.875	0.134	<0.001
N injections = 1,022	Week 2 × injection	0.046	0.164	0.781
N patients = 496	Month 2 intercept	–1.265	0.269	<0.001
	Month 2 × injection	–0.516	0.284	0.069
Acute pain and clustered injections	Intercept	6.391	0.090	<0.001
N scores = 790	Index baseline score	0.420	0.050	<0.001
375 baseline	Injection	–0.948	0.157	<0.001
287 2 weeks	Week 2 intercept	–2.047	0.229	<0.001
128 2 months	Week 2 × injection	0.024	0.285	0.934
N injections = 375	Month 2 intercept	–1.636	0.429	<0.001
N patients = 182	Month 2 × injection	–0.811	0.438	0.066

HLM = hierarchical linear model; NRS = numerical rating scale; SE = standard error.

Appendix III

Parameter estimates and significance levels for two-level HLM models of 2-month 50% NRS improvement outcomes

Sample		OR	95% CI	*P* value
Total	Intercept	1.125	0.831,1.524	0.445
N 2-month outcomes = 1,017	Index baseline score	1.001	0.943,1.062	0.978
N patients = 644	Index chronicity	0.688	0.507,0.936	0.017
—	Injection	0.826	0.689,0.989	0.038
Acute pain	Intercept	0.966	0.630,1.480	0.872
N 2-month outcomes = 230	Index baseline score	1.012	0.893,1.146	0.853
N patients = 162	Injection	1.007	0.658,1.542	0.972

CI, confidence interval; HLM = hierarchical linear model; NRS = numerical rating scale; OR, odds ratio.