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Epidural Steroid Injections Are Associated with Less Improvement in the Treatment of Lumbar Spinal Stenosis: A subgroup analysis of the SPORT

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Abstract

Summary of Background Data—Lumbar spinal stenosis is a common incidental finding among adults over the age of 60. The use of ESI in these patients is common, although there is

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little evidence in the literature to demonstrate the long-term benefit of ESI in the treatment of lumbar stenosis.

Objective—The hypothesis of this study was that patients who received epidural steroid injections (ESI) during initial treatment as part of the Spine Patient Outcomes Research Trial (SPORT) would have improved clinical outcomes and a lower rate of crossover to surgery compared to patients who did not receive ESI.

Methods—Patients with lumbar spinal stenosis who received epidural steroid injections within the first three months of enrollment in SPORT (ESI) were compared to patients who did not receive epidural injections during the first three months of the study (No ESI).

Results—There were 69 ESI patients and 207 No-ESI patients. There were no significant differences in demographic factors, baseline clinical outcome scores, or operative details although there was a significant increase in baseline preference for nonsurgical treatment among ESI patients (62% vs. 33%, $p < 0.001$). There was an average 26 minute increase in operative time and an increased length of stay by 0.9 days among the ESI patients who ultimately underwent surgical treatment. Averaged over four years, there was significantly less improvement in SF36 PF among surgically treated ESI patients (ESI 14.8 vs. No-ESI 22.5, $p = 0.025$). In addition, there was also significantly less improvement among the nonsurgically treated patients in SF36 BP (ESI 7.3 vs. No-ESI 16.7, $p = 0.007$) and SF36 PF (ESI 5.5 vs. No-ESI 15.2, $p = 0.009$). Of the patients assigned to surgical treatment, there was a significantly increased crossover to nonsurgical treatment among patients who received an ESI (ESI 33% vs. No ESI 11%, $p = 0.012$). Of the patients assigned to non-operative treatment, there was a significantly increased crossover to surgical treatment in the ESI patients (ESI 58% vs. No ESI 32%, $p = 0.003$).

Conclusion—Despite equivalent baseline status, ESI were associated with significantly less improvement at four years among all patients with spinal stenosis in SPORT. Furthermore, ESI were associated with longer duration of surgery and longer hospital stay. There was no improvement in outcome with ESI whether patients were treated surgically or nonsurgically.

Keywords

Epidural Steroid Injection; lumbar stenosis; Nonsurgical Treatment; pain management

Introduction

Lumbar spinal stenosis (LSS) is a common condition in the adult population. Most such patients remain asymptomatic and require no further treatment. For those individuals who develop symptoms, nonoperative treatment is usually successful. Nonoperative treatment of lumbar spinal stenosis (LSS) can include use of analgesic medications, exercise, physical therapy and/or epidural injections. Epidural steroid injections (ESI) represent a common option for nonsurgical treatment of LSS and can be delivered either via an interlaminar or transforaminal route. A survey of spinal surgeons indicates that the majority (69%) consider ESI to represent the first line of invasive treatment for LSS after a course of conservative management has failed to provide significant relief¹. This high rate of ESI use continues despite conflicting reports as to the efficacy of this treatment in randomized, controlled trials²⁻⁴ and a recent report casting doubt on the cost-effectiveness of ESI⁵.

Establishing the effectiveness of epidural steroid injections in leading to better long term outcomes and avoiding surgery among those with symptomatic LSS would be important to patients, clinicians and policymakers. Therefore, this study sought to describe the impact of ESI on clinical outcome among patients from the SPORT study with lumbar spinal stenosis; patients were included regardless of final treatment rendered (operative or non-operative). Based on the previous positive studies of the impact of ESI, the *a priori* hypothesis of this

subgroup analysis was that patients who received epidural injections would have significantly improved outcomes and increased surgical avoidance (increased crossover from surgical to nonsurgical treatment and reduced crossover from nonsurgical treatment to surgery) compared to patients who did not receive epidural injections.

Methods

Study Design

SPORT was conducted at 13 multidisciplinary spine practices in eleven states. The institutional review boards at each center approved the standardized protocol. The SPORT included a randomized cohort and a concurrent observational cohort. In this study, the patients from the randomized and observational cohorts were combined into a single study. The methods used to study the lumbar stenosis cohort of the SPORT trial have been detailed in previous reports.^{6, 7} The plausibility of the observed effects was reviewed using a set of established guidelines for the interpretation of subgroup analyses. The results of this checklist are reported in Appendix 1.⁸

Patient Population

Inclusion criteria in the SPORT spinal stenosis cohort were neurogenic claudication or radicular leg pain with associated neurological signs, spinal stenosis as seen on cross-sectional imaging, symptoms that had persisted for at least twelve weeks, and physician confirmation that enrolled patients were a surgical candidate should they be randomized to the surgical wing. Exclusion criteria were spondylolysis and/or spondylolisthesis. Enrollment began in March 2000 and ended in February 2005. Patients were offered the choice of enrollment into the prospective, randomized arm or into an observational arm. For the purposes of this study, the randomized and observational cohorts were combined for the purpose of analyzing a single cohort with an “as treated” methodology in large part due to extensive crossover in the randomized cohort.

Study interventions

The protocol surgery consisted of standard posterior laminectomy with or without bilateral partial facetectomy and foraminotomy per the preferences of the treating surgeon. The non-operative protocol was “usual recommended care,” to include ESI, active physical therapy, education and counseling with instructions regarding home exercise, and nonsteroidal anti-inflammatories if tolerated by the patient.

Study Measures

Primary outcome measures were the SF-36^{9, 10} bodily pain and physical function subscores and the AAOS MODEMS version of the ODI¹¹ measured at six weeks, three months, six months and yearly up to 4 years after enrollment. Secondary outcomes included the Stenosis Bothersomeness Index the Low Back Pain Bothersomeness scale and the Leg Pain scale which were recorded at the same time points¹².

Comparison

Patients were divided into three groups (Figure 1). Patients who received epidural injections during the first three months of the SPORT study were categorized as the “ESI” group. Patients who did not receive pre-enrollment ESI or ESI after enrollment were defined as “No ESI.” To fairly assess the effect of ESI, we excluded the patients who had ESI as part of their treatment prior to enrollment in SPORT because these patients may have failed to respond to ESI initially. We also deliberately excluded those who received ESI “later” in

treatment (more than 3 months after enrollment) as these might have been performed as a “salvage intervention” among patients destined to have a poorer outcome.

The primary analyses compared baseline demographic and clinical factors, operative details, and change in the clinical outcome measures within each treatment arm (i.e., surgery or nonoperative) between ESI and no ESI groups. The treatment effect of surgery was the differential improvement in the outcome of surgically decompressed patients and nonsurgically treated patients. Treatment effect of surgery was compared between patients who received ESI and non-ESI.

Statistical modeling was performed with use of SAS software (version 9.1; SAS Institute, Cary, North Carolina), with the procedures PROC MIXED, and S-PLUS software (version 6.2; Insightful, Seattle, Washington) was used for all other calculations. Significance was denoted as $p < 0.05$ on the basis of two-sided hypothesis testing.

Results

The study included 69 patients who received ESI (“ESI”) within the first three months of enrollment and 207 patients who did not receive any ESI (“No ESI”) (Figure 1). Overall 77% (154) of all of the patients who received ESI during the SPORT study period (200) had them within the first three months of enrollment. There were no significant baseline demographic differences between groups in age, gender, ethnicity, race, education, income, marital status, work status, compensation, mean BMI, smoker, or comorbidities. Baseline characteristics and demographics of the ESI cohort are reviewed in Table 1.

There were no statistically significant differences between groups in baseline primary outcome measures (SF36 BP, SF36 PF, SF36 PCS, SF36 MCS, ODI), Stenosis Bothersomeness Index, Back Pain Bothersomeness Scale, Leg Pain Bothersomeness Scale, Satisfaction with Symptoms, or patient self-assessed health trend. There was a trend toward worse baseline Stenosis Frequency Index (ESI 15 vs. No-ESI 13.5, $p=0.051$) in the ESI patients. There was a significant difference in treatment preference at baseline between groups with the ESI patients having a significantly increased preference for non-surgical treatment (ESI 62% vs. No-ESI 33%, $p<0.001$) (Table 1). There were no significant baseline differences between groups in clinical presentation or symptom severity (Pseudoclaudication, SLR, Pain Radiation, Neurological Deficit, Reflexes, Sensory Deficit, Motor Weakness, Stenosis Levels, Stenotic Levels, Stenosis Locations, Stenosis Severity) or percentage of patients who received surgery (Table 1).

Operative treatments, complications, and events are compared between ESI and No ESI groups in Table 2. There were no statistically significant differences in procedure details (decompression vs. fusion), multilevel fusion, laminectomy level, or number of levels decompressed between groups. There were significant differences which favored the No-ESI group in operative time (ESI 142.5 minutes vs. No ESI 116 minutes, $p=0.032$) and length of stay (ESI 3.6 days vs. No ESI 2.7 days, $p=0.021$). There were no statistically significant differences between groups in blood loss, blood replacement, intraoperative blood replacement, post operative transfusion, intraoperative complications (including dural tear), or postoperative complications (hematoma, infection, or other) between groups. Although there were no statistically significant differences in the incidence of fusion between the two groups, a secondary analysis of patients was performed excluding the patients who underwent fusion. There was a trend towards increased operative time in the ESI (112 minutes) vs No-ESI (107.4 minutes, $p=0.66$). There was also a trend towards increased length of stay in the ESI (2.9 days) versus no ESI (2.6 days, $p=0.29$). There were no statistically significant differences between groups in reoperation rate.

Changes in outcome measures over the study period are displayed in Table 3. The change in outcome measures was adjusted for age, gender, marital status, smoking status, race, compensation, herniation, location, work status, stomach comorbidity, depression, self-rated health trend, treatment preference at baseline, baseline score for SF36, ODI, Sciatica Bothersomeness, and symptom duration. Averaged over four years, there was significantly less improvement in surgically treated ESI patients in SF36 PF (ESI 14.8 vs. No ESI 22.5, $p=0.025$) and a trend toward less improvement in SF36 BP (ESI 23.4 vs. No ESI 29.4, $p=0.053$). Over the four year study period, there was significantly less improvement in nonsurgically treated ESI patients in SF36 BP (ESI 7.3 vs. No ESI 16.7, $p=0.007$) and SF 36 PF (ESI 5.5 vs. No ESI 15.2, $p=0.009$). There was a trend toward less improvement in ODI over the four year study period among both surgically (ESI -16.6 vs No-ESI -20.3, $p=0.15$) and nonsurgically (ESI -5.3 vs No ESI -10.2, $p=0.075$) treated patients. There were no significant differences in treatment effect of surgery between the two groups over the study period in any outcome measure.

The adjusted change in primary and secondary outcome measures at each time point is displayed in Table 4 and Figure 2. The longest follow-up available was four years. In the surgically treated ESI patients, there was significantly less improvement at four years in SF36 BP (ESI 18.4 vs. No ESI 28.4, $p=0.042$), ODI (ESI -11.7 vs. No ESI -19.7, $p=0.033$), and a trend in SF36 PCS (ESI 4.5 vs 8.6, $p=0.051$). Furthermore, there was significantly less improvement at four years in surgically treated ESI patients in secondary outcome measures such as Sciatica Bothersomeness Index (ESI -5.8 vs. No ESI -8.8, $p=0.032$) and patient satisfaction (ESI 41.9 vs. No ESI 70.9, $p=0.019$). In the nonsurgically treated ESI patients, there was significantly less improvement at four years in SF36 BP (ESI 3.7 vs. No ESI 16.6, $p=0.023$), SF36 PF (ESI 0.9 vs. No ESI 15.2, $p=0.011$), SF36 PCS (ESI -0.2 vs. No ESI 6.5, $p=0.004$). There was a trend toward less improvement in the nonsurgically treated patients in ODI at four years (ESI -5.7 vs No ESI -11.7, $p=0.17$). There were no significant differences in secondary outcome measures in between ESI and No-ESI groups treated nonsurgically at 1,2,3, or 4 year time points. There were no significant differences in treatment effect of surgery at four years.

Crossover from assigned or chosen treatment at enrollment to final treatment is displayed in Table 5. Of the patients assigned to surgical treatment, there was a significantly increased crossover to nonsurgical treatment among patients who received an ESI (ESI 33% vs. No ESI 11%, $p=0.012$). Of the patients assigned to non-operative treatment, there was a significantly increased crossover to surgical treatment in the ESI patients (ESI 58% vs. No ESI 32%, $p=0.003$).

The results of the entire ESI ($n=452$) vs No ESI ($n=182$) cohorts are reported in Table 6. At baseline, there was significantly lower incidence of patient satisfaction in the ESI cohort (71% vs 62%, $p=0.026$). There was an increased incidence of pain radiation in the ESI cohort (82% vs 71%, $p=0.006$), any neurological deficit (ESI 58% vs No ESI 47%, $p=0.016$). There was a higher percentage of patients with asymmetric motor (ESI 31% vs No-ESI 20%, $p=0.005$) and reflex (ESI 29% vs No-ESI 19%, $p=0.011$) abnormalities in the total ESI population at baseline. This difference in motor weakness and reflex abnormalities was not reflected in physical function score differences between ESI and no ESI groups (SF36 PF domain or ODI). Operative details for the entire ESI cohort are reported in Table 7. In the ESI patients, there was an increased operative time (ESI 135 minutes vs No-ESI 115 minutes, $p=0.006$) and increased length of stay (ESI 3.4 days vs No ESI 2.7 days, $p=0.003$). Average change in outcome for all of the ESI and No-ESI patient is reported in Table 8 at each time point and in Table 9 for aggregate area-under-the-curve results. There was significantly less improvement in surgically treated ESI patients in SF36 BP (ESI 26.8 vs No ESI 31.5, $p=0.014$) and sciatica bothersomeness index (ESI -6.8 vs No ESI -8.1,

p=0.012). There was statistically significantly less improvement in nonsurgically treated ESI patients in SF36 BP (ESI 12.1 vs No-ESI 18.8, p=0.004), SF36 PF (ESI 9.4 vs No-ESI 16.3, p=0.003). There was no statistically significant difference in crossover associated with ESI (Table 10).

Discussion

These results demonstrate significantly less improvement in the ESI patients whether treated surgically or nonsurgically over the four year study period. There was also increased operative time and increased length of hospital stay in the ESI patients. Despite the common treatment practice of incorporating one or more ESI in the initial nonoperative management of patients with spinal stenosis, these results suggest that ESI is associated with worse outcome in the treatment of spinal stenosis.

These results are in contrast to the previous ESI literature. Several previous studies have demonstrate improved outcome after ESI, although many ESI studies in the historical literature are uncontrolled studies from which it is difficult to separate the waxing/waning natural history of spinal stenosis and any potential treatment effect. For instance, Briggs *et al.*¹³ in a prospective observational study recently demonstrated a declining benefit to ESI in patients with lumbar stenosis at 1 and 3 months and showed greater efficacy in patients with better emotional health and those who were obese, but the study was limited by the lack of any control group. In a retrospective study with telephone follow-up of 3 years, Lee *et al.*¹⁴ demonstrated that while 70% of patients had recurrent symptoms and less than half would undergo the procedure again, nearly 40% reported lasting relief at final follow-up although no outcome predictors of success could be identified. This study also did not include a control group. A prospective randomized controlled study performed by Koc *et al.*¹⁵ demonstrated improved functional outcomes at 6 months in patients treated with ESI versus a control group of patients treated with nonsteroidal anti-inflammatory medications and home exercise. Riew *et al.*² performed a prospective, randomized, controlled study of ESI vs. injection with local anesthetic alone. The authors demonstrated greater surgical avoidance in the group treated with ESI at a final follow-up that averaged 23 months. The study cohort, however, was composed of patients with either spinal stenosis or lumbar disc herniation and the data are not sufficiently broken down by diagnosis to ascertain if surgical avoidance was found only among the patients with disc herniations, spinal stenosis, or only among the aggregate group. A recent update from the same investigators¹⁶ with a minimum follow-up of 5 years found that 17/21 patients continued to avoid surgery although the difference previously found in surgical avoidance between patients treated with ESI and those treated with a local anesthetic only was no longer significant. However, there was no long term difference in **NASS outcome score** associated with ESI. Cuckler *et al.*¹⁷ found no lasting benefit to ESI in a randomized, prospective trial at an average follow-up of 20 months, classifying more than 2/3 of lumbar stenosis patients who received ESI as treatment failures and demonstrating no benefit to performing a second injection in cases where the first was ineffective in alleviating symptoms. Fukusaki *et al.*¹⁸ found no difference in walking distance between patients treated with local anesthetic injection and ESI in a prospective, randomized controlled trial with a follow-up of 3 months. At final follow-up, both the local anesthetic and ESI groups each had good or excellent results in only ~5% of enrolled patients. In a large retrospective study, Friedly *et al.*¹⁹ similarly demonstrated increased rates of surgical intervention and opioid use after ESI after follow-up of 6 months in more than 10,000 patients with spinal stenosis.

In contrast to some of the previous studies, we studied a prospectively collected, large study population with a single anatomical and clinical diagnosis and well defined inclusion and exclusion criteria. Previous studies often mix patients with spinal stenosis with degenerative

spondylolisthesis, whereas this study excluded patients with spondylolisthesis or instability.^{20, 21} We included only patients who did not receive ESI prior to enrollment in SPORT to avoid a potential confounder from a treatment failure of an early epidural injection prior to enrollment in the study or from a later ESI given as a salvage procedure after failing other nonoperative treatments. The effect was observed in several different general and disease-specific outcome measures including SF36 and Bothersomeness Index. However, this effect was not observed in ODI, a lumbar spine specific outcome measure. Furthermore, this study compares injection versus non-injection as a methodology, in contrast to most studies which evaluate the effect of injection versus placebo injection. Several previous studies have relied on administrative databases using CPT and ICD coding which may not be as precise for identification of symptomatic spinal stenosis and exclusion of patients with spondylolisthesis. This study also includes patients treated surgically and nonsurgically, which enables estimation of the treatment effect of surgery and analysis of the results of epidural injections after both surgical and nonsurgical treatment. Additionally, this is one of the first studies to include baseline assessment of treatment preference (surgical or nonsurgical treatment) in the context of analysis of “surgical avoidance.” We suspect that baseline treatment preference is associated with crossover from assigned treatment and may confound previous analyses of surgical avoidance. These results confirm that patients who underwent ESI had a preference for nonsurgical treatment at baseline. Other studies which evaluate surgical avoidance associated with ESI do not include an analysis of baseline patient preference.² Lastly, our study population is one of the largest cohorts with individual patient data, as opposed to aggregate data, and contains the longest follow-up in the literature describing the use of ESI in patients with spinal stenosis.

There are several possibilities for the poor outcome after ESI which we observed in this study. We hypothesize that the most likely explanation is that the additional volume of the ESI and/or steroid material exacerbates the underlying central stenosis and radiculopathy. It is possible that the mass effect of adding steroid and local anesthetic volume to a stenotic spinal canal may exacerbate symptoms of spinal stenosis after the immediate palliative effects of the injection have dissipated. ESI have also been hypothesized to exacerbate epidural lipomatosis in some circumstances which could exacerbate spinal stenosis in the long term.^{22, 23} Another possible explanation is that the ESI may temporarily mask protective painful stimuli and otherwise disinhibit patients who would be limited by pain. Thus ESIs may temporarily diminish pain, but may actually potentiate damage to the nerve roots in the long term which ultimately diminishes clinical outcomes even after a successful decompression operation. Other possible explanations for poor results after ESI include the possibility of nerve injury or scarring from toxicity of the lidocaine, corticosteroid, or carrier agent. Local anesthetics and preservatives in corticosteroids have been demonstrated to be toxic after intraarticular injections^{24, 25} and more recently in culture with intervertebral disc cells²⁶. It is possible that subtle toxicity of the steroids²⁷⁻²⁹ or local anesthetics directly injure neuronal³⁰⁻³² or glial elements.³³ We feel that these results call for further detailed study of the biological effects of ESI.

These results provide conflicting data on surgical avoidance after ESI. Of the patients who were assigned or chose surgery, there was an increased percentage of patients who crossed over to nonsurgical treatment among the ESI patients (33%) compared to the non-ESI patients (11%, $p=0.012$). However, of the patients who were designated to undergo nonsurgical treatment, there was an increased percentage who elected to undergo surgical intervention among the ESI patients (58%) compared to No-ESI patients (32%, $p=0.003$). Therefore, ESI were associated with increased crossover both to and from surgical intervention. Since there was less improvement in the nonsurgically treated patients compared to the surgically treated patients at all time points, some of the patients who crossed over to nonsurgical treatment may have ultimately achieved less improvement in

outcome than they would have otherwise achieved. Our results suggest that patients who received ESI had less improvement after surgery and that surgical ESI patients had longer operative times and longer postoperative lengths of stay than patients who underwent surgery without preoperative ESI. There were no statistically significant differences at baseline between the surgically treated ESI and No-ESI groups in type of surgery, severity of stenosis, number of levels decompressed, and postoperative complications to explain this difference otherwise. One explanation for the inferior results and increased surgical duration is that ESI may result in increased adhesions or scarring, increasing the complexity of surgical decompression. However, the findings of increased operative time and blood loss was unexpected and therefore may be coincidental and unrelated to ESI. There were trends to suggest an increased incidence of multilevel fusions and instrumented fusions in the ESI patients which we acknowledge may confound the analysis of operative time, particularly in the absence of a finding such as increased dural tear rate which may be more directly related to the ESI. The secondary analysis to exclude patients who underwent fusion did not display a trend in difference in operative time between groups.

A limitation of this study includes the fact that this is a retrospective subgroup analysis of prospectively collected data and was not an a priori specified subgroup analysis. The technique of administration of epidural injections was heterogenous, although a recent study suggests there no significant differences in outcome based on the ESI technique³⁴. Furthermore, we do not have information on whether the injections were fluoroscopically guided or the nature of the corticosteroid administered (particulate vs. non-particulate). Therefore, there may be technical modifications to the parameters which could be investigated in future studies to improve outcome of patients with ESI. However, the technique of these injections reflects the actual state of clinical practice at 13 spine centers across the United States. Therefore, if significant technical heterogeneity exists then the authors would assume that this reflects the ambiguity that exists in clinical practice. The authors would also expect that technical heterogeneity would bias the results towards no difference in outcome, not less improvement. There are other limitations which are common to subgroup analyses of prospective, randomized studies.⁸ Since patients were not randomized to epidural vs no-epidural treatment, there is the possibility of an unknown confounder biasing the results. Although the known common confounding variables (age, workman's compensation status, duration of symptoms, obesity, smoking, etc) were not statistically significantly different between groups (Table 1), we acknowledge the possibility that an unknown confounder possibly unrelated to the epidural steroid injections (such as sagittal imbalance) may have influenced results and produced a type I error. One such possible confounder is selection bias in epidural injections. We do not have information about the factors that influenced patients to receive epidural injections, other than patient preference at enrollment. The only plausible factor that we identified at baseline to distinguish who received an epidural steroid injection was a statistically significant preference for nonsurgical treatment at baseline in the ESI patients. It is plausible that this baseline preference may reflect risk averse behavior which may confound the outcome of both surgical and nonsurgical treatment.

Another possible confounder is the limitation of the study population to patients who received epidural injections within three months. This decision was made prior to review of the data to exclude patients who received epidurals as a salvage intervention after a failed attempt at nonsurgical treatment late in the study. Similarly, patients who had received ESIs prior to enrollment were also excluded due to concerns about including patients with failed initial interventions. To inform readers of whether this population reflects the larger population of patients who received ESI, baseline variables and change in outcome of all patients who received ESIs are reported in Tables 6,7,8,9, and 10. As suspected, the entire ESI cohort was similar to the subset study population with lower patient satisfaction at

baseline but similar pain scores at baseline. Similar to the 3 month subset study population, the total ESI cohort of patients had statistically significantly less improvement in pain over the study period. Since the difference in outcome was also observed in the larger group of patients who received epidurals during the SPORT study as well as the initial study cohort (3 months), we believe that the effect observed is consistent and disproves selection bias between the groups.

In conclusion, patients with spinal stenosis who received ESI had significantly less improvement in outcome. There was no distinct surgical avoidance noted with ESI. Our data suggests that an intrinsic property of the ESI is likely causative as this effect was seen in both surgical and nonsurgical patients. Further prospective research is necessary to understand the indications and results of this common procedure.

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Appendix

Subgroup Analysis Checklist from Sun et al⁸

Is the subgroup variable a characteristic measured at baseline or after randomisation?*	The variable (epidural steroid injection) was specified at baseline. We specifically excluded patients who received late epidural steroid injections to avoid this effect.
Is the effect suggested by comparisons within rather than between studies?	Yes. Absolutely. The effect was not observed from combining studies (such as SPORT spinal stenosis, disk herniation, and degenerative spondylolisthesis)
Was the hypothesis specified a priori?	Yes. It is explicitly stated in the introduction.
Was the direction of the subgroup effect specified a priori*	Yes. This is explicitly stated in the introduction. However, the direction of the effect is opposite that which we hypothesized, it is not implausible given recent biological and clinical information on injection agent toxicity.
Was the subgroup effect one of a small number of hypothesised effects tested?	Yes
Does the interaction test suggest a low likelihood that chance explains the apparent subgroup effect?	Yes. We specifically evaluated for common potential confounders of outcome of treatment of lumbar stenosis (age, workmans' compensation status, obesity, etc displayed in Table 1) and found no difference in incidence of confounders. Furthermore, the outcome scores were balanced at baseline between groups.
Is the significant subgroup effect independent?*	To enhance the independence, a regression analysis was run to analyze the change in outcome adjusting for baseline variables which would be expected to confound outcome. This was explicitly stated in the methods section.
Is the size of the subgroup effect large?	Yes. The difference reported in the subgroup effect is large (6 points SF36 BP, 8 points SF36 PF, 4 points ODI) that is likely both statistically and clinically significant.
Is the interaction consistent across studies? •	There are no other studies that specifically report the change in outcome four years after epidural versus no epidural injection treatment. There are studies that report outcome after corticosteroid versus local anesthetic alone but this is different from our study model.
Is the interaction consistent across closely related outcomes within the study?*	Yes. The effect (less improvement in outcome in ESI patients) is noted in both primary and secondary outcome measures at several time points.

Is there indirect evidence that supports the hypothesised interaction (biological rationale)?

Yes. There is a significant literature reporting toxicity of local anesthetics and carrier agents in musculoskeletal applications. Furthermore, epidural steroid injections have been shown to be associated with epidural lipomatosis in other studies (see discussion)

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Key Points

The study evaluated whether patients with spinal stenosis who received epidural steroid injections (ESI) had improved outcome and surgical avoidance compared to patients who did not receive ESI.

ESI were associated with significantly less improvement at four years among all patients with spinal stenosis in SPORT.

Of the surgically treated patients, ESI were associated with longer duration of surgery and longer hospital stay. ESI were not associated with long term surgical avoidance.

Figure 1.

Study design of SPORT subgroup analysis. Patients from the SPORT spinal stenosis cohort were combined into an “as treated” analysis. The study population includes patients who did not receive epidural injections prior to enrollment in the study.

Figure 2.
Change in primary outcome measures between ESI and No-ESI surgically treated and nonsurgically treated patients.

Table 1

Patient Baseline Demographic Characteristics, Comorbid Conditions, Clinical Findings, and Health Status Measures.

Preenrollment-ESI-No			
Characteristics SPS (RCT & OBS)	No-ESI (n=207)	ESI* (n=69)	p-value
Mean Age (SD)	64.5 (11.6)	66 (9.5)	0.32
Female - no.(%)	69 (33%)	27 (39%)	0.47
Ethnicity: Not Hispanic [†]	198 (96%)	65 (94%)	0.87
Race - White [†]	173 (84%)	60 (87%)	0.63
Education - At least some college	126 (61%)	45 (65%)	0.62
Income - Under \$50,000	33 (16%)	18 (26%)	0.089
Marital Status - Married	151 (73%)	50 (72%)	0.94
Work Status			0.34
Full or part time	61 (29%)	28 (41%)	
Disabled	20 (10%)	4 (6%)	
Retired	107 (52%)	31 (45%)	
Other	19 (9%)	6 (9%)	
Compensation - Any [‡]	14 (7%)	3 (4%)	0.66
Mean Body Mass Index (BMI), (SD) [§]	29 (5.5)	30.3 (4.9)	0.085
Smoker	16 (8%)	2 (3%)	0.26
Comorbidities - no.(%)			
Hypertension	87 (42%)	26 (38%)	0.62
Diabetes	31 (15%)	10 (14%)	0.92
Osteoporosis	19 (9%)	3 (4%)	0.30
Heart Problem	59 (29%)	21 (30%)	0.88
Stomach Problem	34 (16%)	18 (26%)	0.11
Bowel or Intestinal Problem	31 (15%)	8 (12%)	0.62
Depression	19 (9%)	11 (16%)	0.18
Joint Problem	119 (57%)	35 (51%)	0.40
Other [¶]	66 (32%)	23 (33%)	0.94
Time since most recent episode > 6 months	112 (54%)	34 (49%)	0.58
SF-36 scores, mean (SD) ^{††}			
Bodily Pain (BP) Score	35.6 (20.4)	33.1 (17.5)	0.36
Physical Functioning (PF) Score	37.7 (24.8)	36.3 (20.1)	0.66
Mental Component Summary (MCS) Score	50.5 (11.4)	50.2 (12.2)	0.84
Physical Component Summary (PCS)	30.5 (9.3)	29.7 (7)	0.55
Oswestry (ODI) (SD) ^{‡‡}	40.2 (19.9)	42.8 (16)	0.32
Stenosis Frequency Index (0-24) ^{§§}	13.5 (5.7)	15 (4.9)	0.051

Preenrollment-ESI-No			
Characteristics SPS (RCT & OBS)	No-ESI (n=207)	ESI* (n=69)	p-value
Stenosis Bothersome Index (0-24) ^{§§}	14.3 (5.7)	15.2 (4.8)	0.25
Back Pain Bothersomeness (0-6)(SD) ^{¶¶}	4 (1.9)	4.3 (1.5)	0.23
Leg Pain Bothersomeness (0-6)(SD) ^{¶¶}	4.1 (1.8)	4.6 (1.6)	0.06
Satisfaction with symptoms - very dissatisfied	130 (63%)	47 (68%)	0.51
Patient self-assessed health trend - no.(%)			0.64
Getting better	10 (5%)	4 (6%)	
Staying about the same	76 (37%)	21 (30%)	
Getting worse	119 (57%)	43 (62%)	
Treatment preference at baseline - no.(%)			<0.001
Preference for non-surg	68 (33%)	43 (62%)	
Not sure	47 (23%)	15 (22%)	
Preference for surgery	92 (44%)	11 (16%)	
Pseudoclaudication - Any	159 (77%)	57 (83%)	0.40
SLR or Femoral Tension	31 (15%)	15 (22%)	0.26
Pain radiation - any	145 (70%)	52 (75%)	0.49
Any Neurological Deficit	99 (48%)	36 (52%)	0.63
Reflexes - Asymmetric Depressed	41 (20%)	19 (28%)	0.24
Sensory - Asymmetric Decrease	55 (27%)	19 (28%)	1
Motor - Asymmetric Weakness	49 (24%)	17 (25%)	1
Stenosis Levels			
L2-L3	65 (31%)	21 (30%)	1
L3-L4	141 (68%)	44 (64%)	0.60
L4-L5	186 (90%)	65 (94%)	0.40
L5-S1	52 (25%)	17 (25%)	0.94
Stenotic Levels (Mod/Severe)			0.39
None	5 (2%)	2 (3%)	
One	67 (32%)	30 (43%)	
Two	88 (43%)	24 (35%)	
Three+	47 (23%)	13 (19%)	
Stenosis Locations			
Central	181 (87%)	59 (86%)	0.84
Lateral Recess	167 (81%)	60 (87%)	0.32
Neuroforamen	66 (32%)	27 (39%)	0.34
Stenosis Severity			0.91
Mild	5 (2%)	2 (3%)	
Moderate	88 (43%)	31 (45%)	
Severe	114 (55%)	36 (52%)	

Characteristics SPS (RCT & OBS)	Preenrollment-ESI-No		
	No-ESI (n=207)	ESI* (n=69)	p-value
Received surgery**	136 (66%)	42 (61%)	0.56

[†] Race or ethnic group was self-assessed. Whites and blacks could be either Hispanic or non-Hispanic.

[‡] This category includes patients who were receiving or had applications pending for workers compensation, Social Security compensation, or other compensation.

[§] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[¶] Other = problems related to stroke, cancer, fibromyalgia, CFS, PTSD, alcohol, drug dependency, lung, liver, kidney, blood vessel, nervous system, migraine or anxiety.

^{††} The SF-36 scores range from 0 to 100, with higher score indicating less severe symptoms.

^{‡‡} The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less severe symptoms.

^{§§} The Sciatica Bothersomeness index range from 0 to 24, with lower scores indicating less severe symptoms.

^{¶¶} The Low Back Pain Bothersomeness Scale and Leg Pain Bothersomeness scale range from 0 to 6, with lower scores indicating less severe symptoms

^{*} Had ESInjection is defined as received epidural steroid injections at 6 week or 3 months during treatment.

^{**} Patients received surgery were classified according to whether they received surgical treatment during the first 4 years of enrollment.

Table 2

Operative treatments, complications and events.

Preenrollment-ESI-No			
Characteristics SPS (RCT & OBS)	No-ESI (n=134)	ESI (n=41)	p-value
Procedure, no. (%)			0.40
Decompression only	120 (91%)	33 (85%)	
Non-instrumented fusion	6 (5%)	2 (5%)	
Instrumented fusion	6 (5%)	4 (10%)	
Multi-level fusion, no. (%)	5 (4%)	4 (10%)	0.26
Laminectomy Level, no. (%)			
L2-L3	51 (39%)	11 (27%)	0.23
L3-L4	92 (70%)	27 (66%)	0.79
L4-L5	123 (93%)	39 (95%)	0.94
L5-S1	46 (35%)	12 (29%)	0.64
Levels decompressed, no. (%)			0.59
0	2 (1%)	0 (0%)	
1	29 (22%)	12 (29%)	
2	43 (32%)	14 (34%)	
3+	60 (45%)	15 (37%)	
Operation time, minutes (SD)	116 (61.5)	142.5 (86.8)	0.032
Blood loss, cc (SD)	308.9 (383)	395.2 (773.1)	0.34
Blood Replacement, no. (%)			
Intraoperative replacement	10 (8%)	6 (15%)	0.27
Post-operative transfusion	4 (3%)	3 (7%)	0.45
Length of hospital stay, days (SD)	2.7 (1.8)	3.6 (2.6)	0.021
Intraoperative complications [§]			
Dural tear/spinal fluid leak	9 (7%)	6 (15%)	0.21
Other	2 (1%)	0 (0%)	0.96
None	123 (92%)	35 (85%)	0.36
Postoperative complications/events [¶]			
Wound hematoma	2 (2%)	1 (2%)	0.77
Wound Infection	4 (3%)	1 (2%)	0.74
Other	7 (5%)	4 (10%)	0.51
None	117 (89%)	33 (80%)	0.28
Additional surgeries (1-year rate) //	10 (7%)	2 (5%)	0.55
Additional surgeries (2-year rate) //	13 (10%)	3 (7%)	0.62
Additional surgeries (3-year rate) //	18 (13%)	4 (10%)	0.52
Additional surgeries (4-year rate) //	22 (16%)	5 (12%)	0.51
Recurrent stenosis/progressive spondylolisthesis	13 (10%)	4 (10%)	

Preenrollment-ESI-No			
Characteristics SPS (RCT & OBS)	No-ESI (n=134)	ESI (n=41)	p-value
Pseudoarthrosis/fusion exploration	0	0	
Complication or Other	8 (6%)	0	
New condition	1	1	

[§]None of the following were reported: aspiration, nerve root injury, operation at wrong level, vascular injury.

[¶]Any reported complications up to 8 weeks post operation. None of the following were reported: bone graft complication, CSF leak, paralysis, cauda equina injury, wound dehiscence, pseudarthrosis.

^{//}One-, two-, three- and four-year post-surgical re-operation rates are Kaplan Meier estimates and p-values are based on the log-rank test. Numbers and percentages are based on the first additional surgery if more than one additional surgery.

Table 3

Average over four years area under the curve results (per year) from adjusted as-treated outcome analysis by utilization of epidural steroid injection (ESI) for SPS Patients Without Pre-enrollment ESI.

<i>SPS Preenrollment-ESI-No</i>	ESI	Surgical	Non-operative	Treatment Effect† (95% CI)
SF-36 Bodily Pain (BP) (0-100) (SE)	No-ESI	29.4 (1.5)	16.7 (1.8)	12.7 (8.5, 16.8)
	ESI	23.2 (2.7)	7.3 (2.9)	15.9 (10.2, 21.6)
	<i>pvalue</i>	<i>0.053</i>	<i>0.007</i>	<i>0.36</i>
SF-36 Physical Function (PF) (0-100) (SE)	No-ESI	22.5 (1.6)	15.2 (1.9)	7.3 (3.3, 11.4)
	ESI	14.8 (2.9)	5.5 (3.1)	9.3 (3.8, 14.8)
	<i>pvalue</i>	<i>0.025</i>	<i>0.009</i>	<i>0.57</i>
Oswestry Disability Index (ODI) (0-100) (SE)	No-ESI	-20.3 (1.2)	-10.2 (1.4)	-10.1 (-13.2, -7)
	ESI	-16.6 (2.2)	-5.3 (2.3)	-11.3 (-15.5, -7)
	<i>pvalue</i>	<i>0.15</i>	<i>0.075</i>	<i>0.65</i>
Sciatica Bothersomeness Index (0-24) (SE)	No-ESI	-8 (0.4)	-4 (0.5)	-4.1 (-5.3, -2.8)
	ESI	-7.2 (0.8)	-3.4 (0.8)	-3.8 (-5.5, -2.1)
	<i>pvalue</i>	<i>0.35</i>	<i>0.57</i>	<i>0.78</i>

Table 4
Change Scores and Treatment Effects for Primary and Secondary Outcomes in the Randomized and Observational SPS Cohorts Combined patients, According to Treatment Received*

Outcome	1-Year			2-Year			3-Year			4-Year		
	SPS Preenrolment	t-ESI-No	ESI	Surgical	Non-operative	Treatment Effect† (95% CI)	Surgical	Non-operative	Treatment Effect† (95% CI)	Surgical	Non-operative	Treatment Effect† (95% CI)
SF-36 Bodily Pain (BP) (0-100) (SE) ††	No-ESI	31.3 (2.3)	16.5 (2.6)	29.8 (2.3)	16.7 (2.8)	13.2 (6.5,19.9)	29.3 (2.2)	17.9 (2.9)	11.4 (4.5,18.3)	28.4 (2.4)	16.6 (3.2)	11.8 (4.1,19.4)
	ESI	28.3 (4.4)	10.7 (4.1)	24.6 (3.7)	9.4 (4.2)	15.2 (5.6,24.9)	22 (4.2)	6 (4.7)	16 (4.7,27.2)	18.4 (4.4)	3.7 (4.6)	14.7 (3.2,26.1)
	pvalue	0.56	0.24	0.23	0.15	0.73	0.12	0.032	0.49	0.042	0.023	0.68
SF-36 Physical Function (PF) (0-100) (SE) ††	No-ESI	27.6 (2.3)	15.1 (2.6)	22.8 (2.3)	17.3 (2.7)	5.5 (-0.9,11.9)	20.2 (2.2)	15 (2.9)	5.2 (-1.4,11.7)	18.7 (2.4)	15.2 (3.2)	3.5 (-3.8,10.8)
	ESI	20.8 (4.4)	7.7 (4.1)	13.6 (3.8)	7.7 (4.2)	5.9 (-3.3,15)	12.8 (4.2)	4.4 (4.7)	8.4 (-2.3,19.1)	13.5 (4.3)	0.9 (4.6)	12.6 (1.8,23.4)
	pvalue	0.19	0.13	0.037	0.059	0.95	0.12	0.055	0.61	0.29	0.011	0.17
Mental Component Summary (MCS) (0-100) (SE) ††	No-ESI	3.7 (0.9)	0.6 (1.1)	2.6 (0.9)	0.5 (1.2)	2.1 (-0.8,4.9)	1.3 (0.9)	-0.3 (1.2)	1.6 (-1.3,4.6)	1.8 (1)	-0.6 (1.4)	2.3 (-1.5,6)
	ESI	3.6 (1.8)	3.1 (1.7)	2.2 (1.6)	1.1 (1.8)	1.1 (-3.5,2)	2.9 (1.8)	2.9 (2)	0 (-5.4,9)	2.2 (1.9)	1 (1.9)	1.2 (-3.8,6.1)
	pvalue	0.97	0.21	0.84	0.80	0.71	0.44	0.17	0.56	0.84	0.50	0.69
Physical Component Summary (PCS) (0-100) (SE) ††	No-ESI	10.9 (0.9)	5.6 (1.1)	9.5 (0.9)	6.1 (1.1)	3.5 (0.8,6.1)	9 (0.9)	5.8 (1.2)	3.2 (0.4,6)	8.6 (1)	6.5 (1.3)	2.1 (-1.5,2)
	ESI	9.8 (1.8)	3.3 (1.7)	7.1 (1.6)	3.4 (1.7)	3.7 (-0.1,7.6)	5.3 (1.8)	1 (2)	4.3 (-0.3,8.9)	4.5 (1.8)	-0.2 (1.9)	4.8 (0.1,9.4)
	pvalue	0.60	0.27	0.18	0.19	0.90	0.062	0.038	0.69	0.051	0.004	0.34
Oswestry Disability Index (ODI) (0-100) (SE) ††	No-ESI	-22.1 (1.7)	-11.2 (2)	-20.9 (1.7)	-11 (2.1)	-9.9 (-14.8,-5.1)	-18.7 (1.7)	-8.6 (2.2)	-10 (-15,-5)	-19.7 (1.8)	-11.7 (2.4)	-8 (-13.6,-2.4)
	ESI	-21.8 (3.3)	-5.1 (3.1)	-17.2 (2.9)	-4.8 (3.2)	-12.4 (-19.5,-5.3)	-15.4 (3.2)	-7.5 (3.5)	-7.9 (-16.1,0.3)	-11.7 (3.3)	-5.7 (3.5)	-6 (-14.3,2.4)
	pvalue	0.95	0.10	0.21	0.11	0.57	0.37	0.78	0.66	0.033	0.17	0.69
Sciatica Bothersomeness Index (0-24) (SE) ††	No-ESI	-9.4 (0.6)	-4.1 (0.7)	-8.6 (0.6)	-4.7 (0.7)	-3.9 (-5.7,-2)	-8.3 (0.6)	-4.7 (0.8)	-3.6 (-5.5,-1.7)	-8.8 (0.7)	-4.3 (0.9)	-4.6 (-6.7,-2.5)
	ESI	-8.9 (1.2)	-3.2 (1.1)	-7.3 (1)	-3.7 (1.2)	-3.6 (-6.3,-1)	-9.1 (1.2)	-5.1 (1.3)	-3.9 (-7.1,-0.8)	-5.8 (1.2)	-3.8 (1.3)	-2.1 (-5.3,1.1)
	pvalue	0.67	0.49	0.84	0.46	0.87	0.56	0.79	0.84	0.032	0.75	0.19
Low Back Pain Bothersomeness (0-6) (SE) ††	No-ESI	-2.1 (0.2)	-1.1 (0.2)	-2.1 (0.2)	-1 (0.2)	-1.1 (-1.6,-0.6)	-2 (0.2)	-1 (0.2)	-1 (-1.5,-0.5)	-1.8 (0.2)	-1 (0.2)	-0.8 (-1.4,-0.2)
	ESI	-2.3 (0.3)	-1.1 (0.3)	-1.9 (0.3)	-1.1 (0.3)	-0.8 (-1.6,0)	-2.2 (0.3)	-1.2 (0.4)	-1 (-1.9,-0.1)	-1.3 (0.3)	-1.3 (0.3)	0 (-0.9,0.9)
	pvalue	0.67	0.49	0.84	0.46	0.87	0.56	0.79	0.84	0.032	0.75	0.19

Outcome		1-Year		2-Year		3-Year		4-Year	
SPS Preenrollmen t-ESI-No	ESI	Treatment Effect [†] (95% CI)		Treatment Effect [†] (95% CI)		Treatment Effect [†] (95% CI)		Treatment Effect [†] (95% CI)	
		Surgical	Non-operative	Surgical	Non-operative	Surgical	Non-operative	Surgical	Non-operative
pvalue		0.62	0.82	0.60	0.88	0.67	0.75	0.20	0.49
No-ESI		73.7	25.8	47.9 (33.9,61.9)	26	70.6	36.1	70.9	37.5
ESI		67.1	25.2	42 (16.9,67)	36.2	64.4	48.3	41.9	22.2
pvalue		0.58	0.95	0.72	0.37	0.57	0.37	0.019	0.25
									0.17
									33.4 (14.8,52)
									19.8 (-6.5,46)
									0.56

^{*} Adjusted for center, age, gender, baseline score, income, treatment preference, duration of symptoms, compensation, smoking status, BMI, baseline Sciatica Bothersomeness, joint, stomach and bowel.

[†] Treatment effect is the difference between the surgical and non-operative mean change from baseline. Analysis is done using a mixed model with a random subject intercept term. Treatment is a time-varying covariate where a patients' experience prior to surgery is attributed to the non-operative arm and time is measured from enrollment and his/her post-surgery outcomes are attributed to the surgical arm and time is measured from time of surgery.

^{††} The SF-36 scores range from 0 to 100, with higher score indicating less severe symptoms.

^{†††} The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less severe symptoms.

^{§§} The Sciatica Bothersomeness index range from 0 to 24, with lower scores indicating less severe symptoms.

^{¶¶} The Low Back Pain Bothersomness Scale ranges from 0 to 6, with lower scores indicating less severe symptoms

Table 5
Crossover of Assigned/Chosen Treatment Groups at Four Years Follow-up Interval for the SPS Patients without Pre-enrollment ESI

SPS Pre-enrollment-ESI-No	No-ESI (n = 207)	ESI (n = 69)	p-value
Assigned/Chosen Surgery Crossover to Nonoperative (%)	13/122 (11%)	7/21 (33%)	0.012
Assigned/Chosen Nonoperative Crossover to Surgery (%)	27/85 (32%)	28/48 (58%)	0.003

* P-values are from the Chi-square test, which tests whether there is a statistically significant difference in crossover between Had ESInjection and No ESInjection groups for the Surgical group and Non-operative group respectively.

Table 6

Patient Baseline Demographic Characteristics, Comorbid Conditions, Clinical Findings, and Health Status Measures.

Characteristics SPS (RCT & OBS) All ESI	Non-ESI (n=182)	ESI* (n=452)	p-value
Mean Age (SD)	64.3 (11.5)	64.7 (11.7)	0.64
Female - no.(%)	61 (34%)	188 (42%)	0.073
Ethnicity: Not Hispanic [†]	174 (96%)	431 (95%)	0.94
Race - White [†]	151 (83%)	382 (85%)	0.72
Education - At least some college	111 (61%)	290 (64%)	0.51
Income - Under \$50,000	30 (16%)	92 (20%)	0.31
Marital Status - Married	135 (74%)	311 (69%)	0.21
Work Status			0.65
Full or part time	57 (31%)	159 (35%)	
Disabled	17 (9%)	43 (10%)	
Retired	92 (51%)	204 (45%)	
Other	16 (9%)	46 (10%)	
Compensation - Any [‡]	12 (7%)	36 (8%)	0.67
Mean Body Mass Index (BMI), (SD) [§]	29.1 (5.7)	29.7 (5.6)	0.27
Smoker	14 (8%)	48 (11%)	0.33
Comorbidities - no.(%)			
Hypertension	76 (42%)	212 (47%)	0.28
Diabetes	28 (15%)	68 (15%)	0.99
Osteoporosis	18 (10%)	42 (9%)	0.93
Heart Problem	51 (28%)	114 (25%)	0.53
Stomach Problem	30 (16%)	109 (24%)	0.046
Bowel or Intestinal Problem	26 (14%)	60 (13%)	0.84
Depression	19 (10%)	51 (11%)	0.87
Joint Problem	104 (57%)	242 (54%)	0.46
Other [¶]	59 (32%)	161 (36%)	0.50
Time since most recent episode > 6 months	102 (56%)	266 (59%)	0.58
SF-36 scores, mean (SD) ^{††}			
Bodily Pain (BP) Score	35.2 (20.9)	32.7 (19.2)	0.15
Physical Functioning (PF) Score	37.3 (24.3)	33.8 (22.8)	0.09
Mental Component Summary (MCS) Score	50 (11.6)	49.1 (12)	0.39
Physical Component Summary (PCS)	30.5 (9.2)	29.4 (8.4)	0.15
Oswestry (ODI) (SD) ^{‡‡}	40.4 (19.9)	43.2 (17.9)	0.082
Stenosis Frequency Index (0-24) ^{§§}	13.8 (5.6)	13.9 (5.9)	0.83
Stenosis Bothersome Index (0-24) ^{§§}	14.6 (5.6)	14.3 (5.8)	0.56

Characteristics SPS (RCT & OBS) All ESI	Non-ESI (n=182)	ESI* (n=452)	p-value
Back Pain Bothersomeness (0-6)(SD)¶¶	4 (1.9)	4.1 (1.8)	0.30
Leg Pain Bothersomeness (0-6)(SD)¶¶	4.2 (1.7)	4.4 (1.7)	0.38
Satisfaction with symptoms - very dissatisfied	112 (62%)	321 (71%)	0.026
Patient self-assessed health trend - no.(%)			0.14
Getting better	8 (4%)	38 (8%)	
Staying about the same	65 (36%)	138 (31%)	
Getting worse	107 (59%)	271 (60%)	
Treatment preference at baseline - no.(%)			0.21
Preference for non-surg	59 (32%)	170 (38%)	
Not sure	42 (23%)	79 (17%)	
Preference for surgery	81 (45%)	202 (45%)	
Characteristics	Non-ESI	ESI*	p-value
Pseudoclaudication - Any	139 (76%)	369 (82%)	0.16
SLR or Femoral Tension	29 (16%)	103 (23%)	0.07
Pain radiation - any	130 (71%)	369 (82%)	0.006
Any Neurological Deficit	86 (47%)	263 (58%)	0.016
Reflexes - Asymmetric Depressed	35 (19%)	133 (29%)	0.011
Sensory - Asymmetric Decrease	48 (26%)	134 (30%)	0.47
Motor - Asymmetric Weakness	36 (20%)	141 (31%)	0.005
Stenosis Levels			
L2-L3	58 (32%)	121 (27%)	0.23
L3-L4	123 (68%)	297 (66%)	0.72
L4-L5	160 (88%)	419 (93%)	0.075
L5-S1	44 (24%)	129 (29%)	0.31
Stenotic Levels (Mod/Severe)			0.55
None	4 (2%)	11 (2%)	
One	61 (34%)	173 (38%)	
Two	77 (42%)	164 (36%)	
Three+	40 (22%)	104 (23%)	
Stenosis Locations			
Central	158 (87%)	385 (85%)	0.68
Lateral Recess	146 (80%)	357 (79%)	0.81
Neuroforamen	53 (29%)	154 (34%)	0.27
Stenosis Severity			0.92
Mild	4 (2%)	11 (2%)	
Moderate	79 (43%)	203 (45%)	
Severe	99 (54%)	238 (53%)	
Received surgery**	121 (66%)	292 (65%)	0.72

[†] Race or ethnic group was self-assessed. Whites and blacks could be either Hispanic or non-Hispanic.

[‡] This category includes patients who were receiving or had applications pending for workers compensation, Social Security compensation, or other compensation.

[§] The body-mass index is the weight in kilograms divided by the square of the height in meters.

[¶] Other = problems related to stroke, cancer, fibromyalgia, CFS, PTSD, alcohol, drug dependency, lung, liver, kidney, blood vessel, nervous system, migraine or anxiety.

^{††} The SF-36 scores range from 0 to 100, with higher score indicating less severe symptoms.

^{‡‡} The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less severe symptoms.

^{§§} The Sciatica Bothersomeness index ranges from 0 to 24, with lower scores indicating less severe symptoms.

^{¶¶} The Low Back Pain Bothersomeness Scale and Leg Pain Bothersomeness scale range from 0 to 6, with lower scores indicating less severe symptoms

^{*} ESI group is received epidural steroid injections at baseline, 6 weeks, 3 months, 6 months, 1 year, 2 years, 3 years, or 4 years during the study period.

^{**} Patients received surgery were classified according to whether they received surgical treatment during the first 4 years of enrollment.

Table 7

Operative treatments, complications and events.

Characteristics	SPS (RCT & OBS)	All ESI	Non-ESI (n=119) [*]	ESI (n=288) [*]	p-value
Specific procedure, no. (%) [‡]					0.79
Decompression only			106 (90%)	246 (88%)	
Non-instrumented fusion			6 (5%)	16 (6%)	
Instrumented fusion			6 (5%)	19 (7%)	
Multi-level fusion, no. (%)			5 (4%)	11 (4%)	0.92
Laminectomy Level, no. (%)					
L2-L3			44 (38%)	101 (36%)	0.82
L3-L4			79 (68%)	200 (71%)	0.58
L4-L5			109 (93%)	260 (92%)	0.90
L5-S1			40 (34%)	112 (40%)	0.36
Levels decompressed, no. (%)					0.83
0			2 (2%)	6 (2%)	
1			26 (22%)	66 (23%)	
2			41 (34%)	86 (30%)	
3+			50 (42%)	130 (45%)	
Operation time, minutes (SD)			115.1 (63.2)	135 (66.2)	0.006
Blood loss, cc (SD)			299.9 (344.4)	316.8 (428)	0.71
Blood Replacement, no. (%)					
Intraoperative replacement			9 (8%)	30 (11%)	0.49
Post-operative transfusion			3 (3%)	17 (6%)	0.24
Length of hospital stay, days (SD)			2.7 (1.6)	3.4 (2.6)	0.003
Intraoperative complications [§]					
Dural tear/spinal fluid leak			9 (8%)	28 (10%)	0.60
Other			2 (2%)	1 (0%)	0.43
None			108 (91%)	257 (90%)	0.93
Postoperative complications/events [¶]					

Characteristics	SPS (RCT & OBS)	All ESI	Non-ESI (n=119) [*]	ESI (n=288) [*]	p-value
Wound hematoma			1 (1%)	3 (1%)	0.71
Wound Infection			4 (3%)	5 (2%)	0.51
Other			5 (4%)	18 (6%)	0.57
None			106 (91%)	245 (86%)	0.27
Additional surgeries (1-year rate)	//				
Additional surgeries (2-year rate)	//				
Additional surgeries (3-year rate)	//				
Additional surgeries (4-year rate)	//				
Recurrent stenosis/progressive spondylolisthesis			12 (10%)	12 (4%)	
Pseudoarthrosis/fusion exploration			0	0	
Complication or Other			7 (5.8%)	11 (3.9%)	
New condition			1 (NE) ^{**}	7 (2.5%)	

^{*} Surgical information was available for 119 Non-ESI and 288 ESI patients.

[†] Specific procedure data was available for 118 Non-ESI and 281 ESI patients.

[§] None of the following were reported: aspiration, nerve root injury, operation at wrong level, vascular injury.

[¶] Any reported complications up to 8 weeks post operation. None of the following were reported: bone graft complication, CSF leak, paralysis, cauda equina injury, wound dehiscence, pseudoarthrosis.

// One-, two-, three- and four-year post-surgical re-operation rates are Kaplan Meier estimates and p-values are based on the log-rank test.

Numbers and percentages are based on the first additional surgery if more than one additional surgery.

^{**} Not estimable

Change Scores and Treatment Effects for Primary and Secondary Outcomes in the Randomized and Observational SPS Cohorts Combined, According to Treatment Received *.

Table 8

Outcome	1-Year			2-Year			3-Year			4-Year		
	ESI			Non-operative			Non-operative			Non-operative		
SPS All ESI	Surgical		Treatment Effect [†] (95% CI)	Surgical		Treatment Effect [†] (95% CI)	Surgical		Treatment Effect [†] (95% CI)	Surgical		Treatment Effect [†] (95% CI)
SF-36 Bodily Pain (BP) (0-100) (SE) ^{††}	Non-ESI	34 (2.4)	15.6 (8.8,22.4)	33.4 (2.3)	20.4 (3)	13.1 (6,20.1)	30.2 (2.3)	20.5 (3.2)	9.7 (2.4,17)	30.4 (2.5)	16.3 (3.4)	14.1 (6.2,22.1)
	ESI	(1.5)	14.9 (10.8,19)	(1.5)	12.2 (1.8)	14.3 (10,18.6)	27.9 (1.5)	12.4 (1.9)	15.5 (10.9,20)	25.2 (1.6)	12.5 (2.1)	12.7 (7.8,17.6)
pvalue	0.043	0.13	0.009	0.019	0.76	0.39	0.029	0.18	0.07	0.34	0.75	
SF-36 Physical Function (PF) (0-100) (SE) ^{††}	Non-ESI	29.9 (2.3)	13.3 (6.9,19.7)	24.1 (2.3)	17.4 (2.9)	6.6 (0.1,13.2)	21.5 (2.2)	16.5 (3.1)	5 (-1.9,11.9)	21 (2.4)	17.6 (3.3)	3.4 (-4,10.8)
	ESI	23.8 (1.4)	14.2 (10.4,18.1)	21.5 (1.4)	11 (1.7)	10.5 (6.5,14.4)	20.8 (1.5)	8.2 (1.8)	12.5 (8.3,16.8)	20.1 (1.6)	9.5 (1.9)	10.6 (6,15.2)
pvalue	0.024	0.025	0.32	0.055	0.32	0.77	0.02	0.062	0.75	0.034	0.099	
Mental Component Summary (MCS) (0-100) (SE) ^{††}	Non-ESI	3.6 (1)	1.5 (-1.4,4.3)	3.2 (1)	2.2 (1.3)	1 (-2.4)	2.1 (0.9)	0 (1.3)	2.1 (-1.5,1)	2 (1)	-0.1 (1.4)	2 (-1.4,5.4)
	ESI	3.5 (0.6)	0.8 (-0.9,2.6)	3.5 (0.6)	1 (0.7)	2.6 (0.8,4.4)	2.8 (0.6)	1.2 (0.8)	1.5 (-0.4,3.5)	2.6 (0.7)	0.4 (0.9)	2.2 (0,4.3)
pvalue	0.99	0.65	0.78	0.38	0.36	0.53	0.42	0.77	0.61	0.78	0.94	
Physical Component Summary (PCS) (0-100) (SE) ^{††}	Non-ESI	11.9 (1)	5.9 (3.1,8.6)	10 (1)	6.2 (1.2)	3.8 (0.9,6.6)	9.3 (0.9)	6.5 (1.3)	2.8 (-0.1,5.8)	9.2 (1)	6.9 (1.4)	2.4 (-0.9,5.6)
	ESI	9.6 (0.6)	5.6 (4.7,3)	8.8 (0.6)	4.4 (0.7)	4.3 (2.6,6)	8.6 (0.6)	3.6 (0.8)	5 (3.1,6.8)	8.2 (0.7)	4 (0.8)	4.2 (2.1,6.2)
pvalue	0.048	0.13	0.26	0.22	0.75	0.52	0.061	0.22	0.37	0.08	0.34	
Oswestry Disability Index (ODI) (0-100) (SE) ^{††}	Non-ESI	-23.5 (1.8)	-11.4 (-16.4,-6.3)	-22.3 (1.8)	-11.5 (2.3)	-10.8 (-16,-5.6)	-19.7 (1.8)	-9.4 (2.4)	-10.4 (-15.8,-4.9)	-21.5 (1.9)	-12.6 (2.6)	-9 (-14.9,-3)
	ESI	-20.1 (1.1)	-12.2 (-15.2,-9.1)	-19.4 (1.1)	-8.6 (1.3)	-10.8 (-14,-7.6)	-18.3 (1.2)	-9.1 (1.4)	-9.2 (-12.6,-5.8)	-17.5 (1.2)	-8.1 (1.5)	-9.4 (-13,-5.7)
pvalue	0.10	0.088	0.15	0.27	0.99	0.48	0.92	0.72	0.067	0.14	0.91	
Sciatica Bothersomeness Index (0-24) (SE) ^{§§}	Non-ESI	-9.6 (0.6)	-5.6 (-7.4,-3.8)	-8.7 (0.6)	-4.2 (0.8)	-4.4 (-6.3,-2.6)	-8.2 (0.6)	-4.3 (0.9)	-3.9 (-5.8,-1.9)	-9 (0.7)	-3.5 (0.9)	-5.5 (-7.6,-3.4)
	ESI	-7.8 (0.4)	-4.3 (-5.5,-3.2)	-7.6 (0.4)	-4 (0.5)	-3.6 (-4.8,-2.4)	-7.3 (0.4)	-4.2 (0.5)	-3.1 (-4.4,-1.8)	-6.8 (0.5)	-4.1 (0.6)	-2.7 (-4.1,-1.3)
pvalue	0.016	0.53	0.13	0.77	0.45	0.22	0.90	0.50	0.004	0.62	0.026	
Low Back Pain Bothersomeness (0-6) (SE) ^{¶¶}	Non-ESI	-2.2 (0.2)	-1.1 (-1.6,-0.6)	-2.4 (0.2)	-1 (0.2)	-1.4 (-1.9,-0.9)	-2.2 (0.2)	-1 (0.2)	-1.2 (-1.8,-0.6)	-2.1 (0.2)	-0.9 (0.3)	-1.2 (-1.8,-0.6)
	ESI	-2 (0.1)	-1.2 (-1.5,-0.9)	-1.9 (0.1)	-0.9 (0.1)	-1 (-1.3,-0.7)	-1.9 (0.1)	-0.9 (0.1)	-0.9 (-1.3,-0.5)	-1.6 (0.1)	-0.9 (0.2)	-0.7 (-1.1,-0.3)

Outcome		1-Year		2-Year		3-Year		4-Year	
SPS All ESI	ESI	Surgical	Non-operative	Treatment Effect [†] (95% CI)	Surgical	Non-operative	Treatment Effect [†] (95% CI)	Surgical	Non-operative
									Treatment Effect [†] (95% CI)
pvalue		0.28	0.80	0.007	0.68	0.18	0.14	0.72	0.23
	Non-ESI	74.1	26	48 (34.2,61.9)	80.2	31.6	48.6 (34.1,63)	73.4	33.3
	ESI	66.4	28.6	37.9 (28.7,47.1)	64.5	27	37.5 (27.9,47.2)	62.3	36.6
Very/somewhat satisfied with symptoms (%)									
pvalue		0.71	0.25	0.003	0.51	0.17	0.06	0.67	0.70

^{*} Adjusted for center, age, gender, baseline score, income, treatment preference, duration of symptoms, compensation, smoking status, BMI, baseline Sciatica Bothersomeness, joint, stomach and bowel.

[†] Treatment effect is the difference between the surgical and non-operative mean change from baseline. Analysis is done using a mixed model with a random subject intercept term. Treatment is a time-varying covariate where a patients' experience prior to surgery is attributed to the non-operative arm and time is measured from enrollment and his/her post-surgery outcomes are attributed to the surgical arm and time is measured from time of surgery.

^{††} The SF-36 scores range from 0 to 100, with higher score indicating less severe symptoms.

^{†††} The Oswestry Disability Index ranges from 0 to 100, with lower scores indicating less severe symptoms.

^{§§} The Sciatica Bothersomeness index range from 0 to 24, with lower scores indicating less severe symptoms.

^{¶¶} The Low Back Pain Bothersomness Scale ranges from 0 to 6, with lower scores indicating less severe symptoms

Table 9

Average over four years area under the curve results (per year) from adjusted as-treated outcome analysis by utilization of epidural steroid injection (ESI).

SPS All ESI	ESI	Surgical	Non-operative	Treatment Effect† (95% CI)
SF-36 Bodily Pain (BP) (0-100) (SE)	Non-ESI	31.5 (1.6)	18.8 (2)	12.7 (8.3, 17)
	ESI	26.8 (1)	12.1 (1.2)	14.7 (12.1, 17.3)
	pvalue	0.014	0.004	0.42
SF-36 Physical Function (PF) (0-100) (SE)	Non-ESI	24.2 (1.6)	16.3 (2)	7.9 (3.7, 12.1)
	ESI	21.3 (1)	9.4 (1.2)	12 (9.5, 14.4)
	pvalue	0.13	0.003	0.091
Oswestry Disability Index (ODI) (0-100) (SE)	Non-ESI	-21.6 (1.3)	-10.9 (1.6)	-10.7 (-14, -7.4)
	ESI	-18.8 (0.8)	-8.2 (0.9)	-10.7 (-12.6, -8.7)
	pvalue	0.067	0.14	0.98
Sciatica Bothersomeness Index (0-24) (SE)	Non-ESI	-8.1 (0.4)	-3.6 (0.5)	-4.5 (-5.7, -3.3)
	ESI	-6.8 (0.3)	-3.5 (0.3)	-3.3 (-4.1, -2.6)
	pvalue	0.012	0.84	0.10

Table 10
Crossover of Assigned/Chosen Treatment Groups at Four Years Follow-up Interval

SPS All ESI	Non-ESI (n = 182)	E SI (n = 452)	p-value
Assigned/Chosen Surgery Crossover to Nonoperative (%)	14/114 (12%)	29/232 (13%)	0.954
Assigned/Chosen Nonoperative Crossover to Surgery (%)	21/68 (31%)	90/220 (41%)	0.138

* P-values are from the Chi-square test, which tests whether there is a statistically significant difference in crossover between Had ESInjection and No ESInjection groups for the Surgical group and Nonoperative group respectively.