Spine

SPINE Volume 38, Number 4, pp 279–291

RANDOMIZED TRIAL

Epidural Steroid Injections Are Associated With Less Improvement in Patients With Lumbar Spinal Stenosis

A Subgroup Analysis of the Spine Patient Outcomes Research Trial

Kris Radcliff, MD,* Christopher Kepler, MD, MBA,* Alan Hilibrand, MD,* Jeffrey Rihn, MD,* Wenyan Zhao, PhD,† Jon Lurie, MD,† Tor Tosteson, MD,† Alexander Vaccaro, MD, PhD,* Todd Albert, MD,* and James Weinstein, MD†

Study Design. Subgroup analysis of prospective, randomized database from the spine patient outcomes research trial (SPORT)

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

Summary of Background Data. The use of epidural steroid injection (ESI) in patients with lumbar spinal stenosis is common, although there is little evidence in the literature to demonstrate its long-term benefi t in the treatment of lumbar stenosis.

Methods. Patients with lumbar spinal stenosis who received ESI within the first 3 months of enrollment in SPORT (ESI) were compared with patients who did not receive epidural injections during the first 3 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 between the groups, although there was a significant increase in baseline preference for nonsurgical treatment among ESI patients (ESI 62% *vs*. no-ESI 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 4 years, there was significantly less improvement in 36-Item Short Form Health Survey (SF-36) Physical Function among surgically treated ESI patients (ESI 14.8 *vs*. no-ESI 22.5, $P = 0.025$). In addition, there was significantly less improvement among the nonsurgically treated patients in SF-36 Body Pain (ESI 7.3 *vs*. no-ESI 16.7, $P = 0.007$) and SF-36 Physical Function (ESI 5.5 *vs*. no-ESI 15.2, $P = 0.009$). Of the patients assigned to the surgical treatment group, 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 the nonoperative treatment group, 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, ESIs were associated with significantly less improvement at 4 years among all patients with spinal stenosis in SPORT. Furthermore, ESIs 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.

Key words: epidural steroid injection, lumbar stenosis, nonsurgical treatment, pain management. **Spine 2013;38:279–291**

Lumbar spinal stenosis (LSS) is a common condition in the adult population. Most patients with LSS remain asymptomatic and require no further treatment. For individuals who develop symptoms, nonoperative treatment is usually successful. Nonoperative treatment of LSS can include the use of analgesic medications, exercise, physical therapy, and/or epidural injections. Epidural steroid injections (ESIs) are often employed in the 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 invasive treatment of LSS after a course of conservative management has failed to provide significant relief.[1] This high rate of ESI use continues

From the *Department of Orthopedic Surgery, Rothman Institute, Thomas Jefferson University, Philadelphia, PA; and †Dartmouth Medical Center, Dartmouth, NH.

Acknowledgement date: November 17, 2011. First Revision date: February 20, 2012. Second Revision date: April 1, 2012. Acceptance date: April 7, 2012.

The manuscript submitted does not contain information about medical device(s)/drug(s).

The National Institute of Arthritis and Musculoskeletal and Skin Diseases (U01-AR45444) and the Office of Research on Women's Health, the National Institutes of Health, and the National Institute of Occupational Safety and Health, Centers for Disease Control and Prevention, funds were received in support of this work.

Relevant financial activities outside the submitted work: royalties, stocks, grants, consultancy, board membership.

Address correspondence and reprint requests to Kris Radcliff, MD, Department of Orthopedic Surgery, Rothman Institute, Thomas Jefferson University, 925 Chestnut St, Philadelphia, PA 19107; E-mail: kris.radcliff@rothmaninstitute.com

DOI: 10.1097/BRS.0b013e31827ec51f

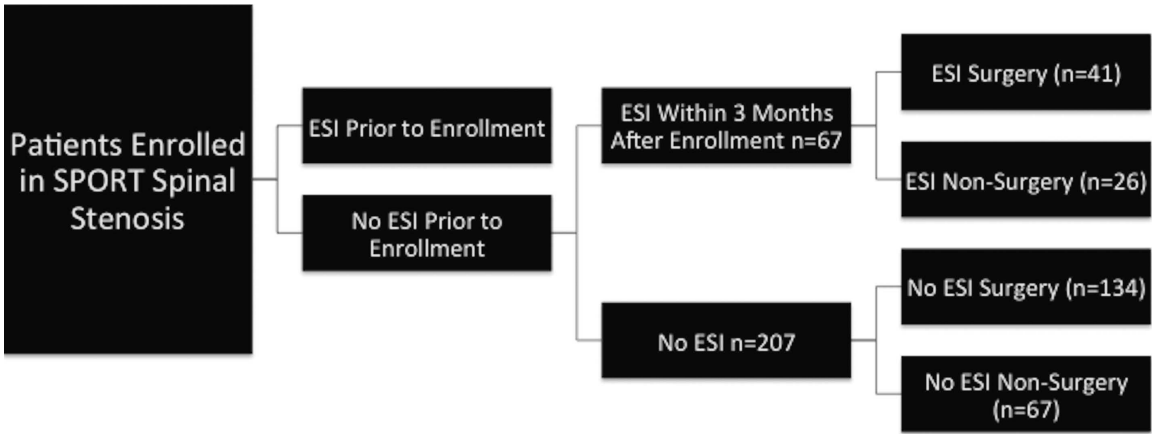

Figure 1. Study design of SPORT subgroup analysis. Patients from the SPORT spinal stenosis cohort were combined into an "as-treated" analysis. The study population includes patients who did not receive epidural injections prior to enrollment in the study. SPORT indicates Spine Patient Outcomes Research Trial.

despite conflicting reports with regard to the efficacy of this treatment in randomized controlled trials,[2–4] and a recent report casting doubt on the cost-effectiveness of ESI.[5]

Establishing the effectiveness of ESI in leading to better long-term outcomes and avoiding surgery among those with symptomatic LSS would be important to patients, clinicians, and policy makers. Therefore, this study sought to describe the impact of ESI on clinical outcome among patients with LSS from SPORT (The Spine Patient Outcomes Research Trial); patients were included regardless of final treatment rendered (operative or nonoperative). On the basis of 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 to surgical treatment) compared with patients who did not receive epidural injections.

MATERIALS AND METHODS

Study Design

SPORT was conducted at 13 multidisciplinary spine practices in 11 states. The institutional review boards at each center approved the standardized protocol. SPORT included a randomized cohort and a concurrent observational cohort. In this subgroup analysis, the patients from the randomized and observational cohorts were combined into a single study. The methods used to study the lumbar stenosis cohort of SPORT have been detailed in previous reports.[6,7] The plausibility of the observed subgroup analyses effects was reviewed using a set of established guidelines for the interpretation of subgroup analyses of prospective, randomized studies. The results of this checklist are reported in Appendix 1 (Supplemental Digital Content 1, available at http://links.lww.com/BRS/A722).[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 12 weeks, and physician confirmation that enrolled patients were surgical candidates 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 the observational arm. For 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 nonoperative protocol was "usual recommended care," including ESI, active physical therapy, education and counseling with instructions regarding home exercise, and nonsteroidal anti-inflammatory drugs if tolerated by the patient.

Study Measures

Primary outcome measures were the 36-Item Short Form Health Survey (SF-36),[9,10] Bodily Pain (BP) and Physical Function (PF) subscale scores, and the AAOS MODEMS version of the Oswestry Disability Index (ODI)[11] measured at 6 weeks, 3 months, 6 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 Bothersomeness Scale, which were recorded at the same time points.[12]

Comparison

Patients were divided into groups according to the timing of ESI (Figure 1). Patients who received epidural injections during the first 3 months of SPORT (and no ESI prior to enrollment in SPORT) were the primary "ESI" study cohort. Patients who did not receive ESI at any point before or during

TABLE 1. Patient Baseline Demographic Characteristics, Comorbid Conditions, Clinical Findings, and Health Status Measures

	Pre-enrollment ESI		
Characteristics SPS (RCT and OBS)	**No-ESI (n = 207)**	**ESI* (n = 69)**	***P***
Age, mean (SD), yr	64.5 (11.6)	66 (9.5)	0.32
Female	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: <$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
Body mass index, mean (SD)§	29 (5.5)	30.3 (4.9)	0.085
Smoker	16 (8%)	2 (3%)	0.26
Comorbidity			
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 mo	112 (54%)	34 (49%)	0.58
SF-36 scores, mean (SD)‖			
BP	35.6 (20.4)	33.1 (17.5)	0.36
PF	37.7 (24.8)	36.3 (20.1)	0.66
MCS	50.5 (11.4)	50.2 (12.2)	0.84
PCS	30.5 (9.3)	29.7 (7)	0.55
ODI, mean (SD)**	40.2 (19.9)	42.8 (16)	0.32
Stenosis Frequency Index (0–24), mean (SD)††	13.5 (5.7)	15 (4.9)	0.051
Stenosis Bothersome Index (0–24), mean (SD)††	14.3 (5.7)	15.2 (4.8)	0.25
Low Back Pain Bothersomeness Scale (0–6), mean (SD)‡‡	4 (1.9)	4.3 (1.5)	0.23
Leg Pain Bothersomeness Scale (0–6), mean (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			0.64
Getting better	10 (5%)	4 (6%)	
Staying about the same	76 (37%)	21 (30%)	

(*Continued*)

TABLE 1. (*Continued*)

Characteristics SPS (RCT and OBS)	Pre-enrollment ESI		
	No-ESI (n = 207)	ESI* (n = 69)	*P*
Getting worse	119 (57%)	43 (62%)	
Treatment preference at baseline			<0.001
Preference for nonsurgery	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 level			
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 level (moderate/severe)			0.39
None	5 (2%)	2 (3%)	
1	67 (32%)	30 (43%)	
2	88 (43%)	24 (35%)	
3+	47 (23%)	13 (19%)	
Stenosis location			
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%)	
Received surgery§§	136 (66%)	42 (61%)	0.56

**Had ESI is defined as received ESIs at 6 week or 3 months during treatment.*

†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.

¶Problems related to stroke, cancer, fibromyalgia, chronic fatigue syndrome, post-traumatic stress disorder, 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 ODI 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 the Leg Pain Bothersomeness Scale range from 0 to 6, with lower scores indicating less severe symptoms.

§§Patients received surgery were classified according to whether they received surgical treatment during the first 4 years of enrollment.

SPS indicates spinal stenosis; RCT, randomized controlled trial; OBS, observational; ESI, epidural steroid injection; SF-36, 36-Item Short Form Health Survey; BP, Body Pain; PF, Physical Function, PCS, Physical Component Summary; MCS, Mental Component Summary; ODI, Oswestry Disability Index; SLR, straight leg raise.

the SPORT study were categorized as the "no-ESI" group. To assess the effect of ESI fairly, we excluded the patients who received 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 (>3 mo after enrollment) because 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 the 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 ESI and non-ESI patients.

Statistical modeling was performed with the SAS software (version 9.1; SAS Institute, Cary, NC), with the procedures PROC MIXED, and the S-PLUS software (version 6.2; Insightful, Seattle, WA) was used for all other calculations. Significance was defined as $P < 0.05$ on the basis of 2-sided hypothesis testing.

RESULTS

The study included 69 patients who received ESI ("ESI") within the first 3 months of enrollment and 207 patients who did not receive any ESI ("no-ESI") (Figure 1). Overall, 77% (154) of the patients who received ESI during the SPORT study period (n = 200) had them within the first 3 months of enrollment. There were no significant baseline demographic differences between groups in age, sex, ethnicity, race, education, income, marital status, work status, compensation, mean body mass index, smoking status, or comorbidities. Baseline characteristics and demographics of the ESI cohort are shown in Table 1.

There were no statistically significant differences between groups in baseline primary outcome measures (SF-36 BP, SF-36 PF, SF-36 Physical Component Summary [PCS], SF-36 Mental Component Summary [MCS], ODI), Stenosis Bothersomeness Index, Low 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 nonsurgical 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, positive straight leg raise, pain radiation, neurological deficit, reflexes, sensory deficit, motor weakness, stenosis levels, stenotic levels, stenosis locations, stenosis severity) or the percentage of patients who received surgery (Table 1).

Operative treatments, complications, and events are compared between the 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 that favored the no-ESI group in operative time (ESI 142.5 min *vs.* no-ESI 116 min, $P = 0.032$) and length of stay (ESI 3.6 d *vs.* no-ESI 2.7 d, $P = 0.021$). There were no statistically significant differences between groups in blood loss, blood replacement, intraoperative blood replacement, postoperative 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 2 groups, a secondary analysis of patients was performed excluding those patients who underwent since fusion can be a confounder of length of stay and operative time. Among the nonfusion patients only, there was a trend toward increased operative time in the ESI group (ESI 112 min *vs.* no-ESI 107.4 min, $P = 0.66$). There was also a trend toward increased length of stay in the ESI (ESI 2.9 d *vs.* no-ESI 2.6 d, $P = 0.29$). There were no statistically significant differences between groups in the reoperation rate.

Changes in outcome measures during the study period are displayed in Table 3. The change in outcome measures was adjusted for age, sex, marital status, smoking status, race, compensation, herniation, location, work status, stomach comorbidity, depression, self-rated health trend, treatment preference at baseline, baseline score for SF-36, ODI, Sciatica Bothersomeness Index, and symptom duration. Averaged over 4 years, there was significantly less improvement in surgically treated ESI patients in SF-36 PF (ESI 14.8 *vs.* no-ESI 22.5, $P = 0.025$) and a trend towards less improvement in SF-36 BP (ESI 23.4 *vs.* no-ESI 29.4, $P = 0.053$). Across the 4-year study period, there was significantly less improvement in nonsurgically treated ESI patients in SF-36 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 during the 4-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 2 groups during 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 4 years. In the surgically treated ESI patients, there was significantly less improvement at 4 years in SF-36 BP (ESI 18.4 *vs.* no-ESI 28.4, $P = 0.042$) and ODI (ESI −11.7 *vs.* no-ESI −19.7, $P = 0.033$) and a trend in SF-36 PCS (ESI 4.5 *vs.* no-ESI 8.6, $P = 0.051$). Furthermore, there was significantly less improvement at 4 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 4 years in SF-36 BP (ESI 3.7 *vs.* no-ESI 16.6, $P = 0.023$), SF-36 PF (ESI 0.9 *vs.* no-ESI 15.2, $P = 0.011$), and SF-36 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

TABLE 2. Operative Treatments, Complications, and Events

Characteristics SPS (RCT and OBS)	Pre-enrollment ESI		
	No-ESI (n = 134)	ESI (n = 41)	*P*
Procedure			0.40
Decompression only	120 (91%)	33 (85%)	
Noninstrumented fusion	6 (5%)	2 (5%)	
Instrumented fusion	6 (5%)	4 (10%)	
Multilevel fusion	5 (4%)	4 (10%)	0.26
Laminectomy level			
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 decompresssed			0.59
0	2 (1%)	0 (0%)	
1	29 (22%)	12 (29%)	
2	43 (32%)	14 (34%)	
3+	60 (45%)	15 (37%)	
Operation time, mean (SD), min	116 (61.5)	142.5 (86.8)	0.032
Blood loss, mean (SD), mL	308.9 (383)	395.2 (773.1)	0.34
Blood replacement			
Intraoperative replacement	10 (8%)	6 (15%)	0.27
Postoperative transfusion	4 (3%)	3 (7%)	0.45
Length of hospital stay, mean (SD), d	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 surgical procedures (1-yr rate)‡	10 (7%)	2 (5%)	0.55
Additional surgical procedures (2-yr rate)‡	13 (10%)	3 (7%)	0.62
Additional surgical procedures (3-yr rate)‡	18 (13%)	4 (10%)	0.52
Additional surgical procedures (4-yr rate)‡	22 (16%)	5 (12%)	0.51
Recurrent stenosis/progressive spondylolisthesis	13 (10%)	4 (10%)	

(*Continued*)

TABLE 2. (*Continued*)

Characteristics SPS (RCT and OBS)	Pre-enrollment ESI		
	No-ESI (n = 134)	ESI (n = 41)	*P*
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 a wrong level, and vascular injury.*

†Any reported complications up to 8 weeks postoperation. None of the following were reported: bone graft complication, cerebrospinal fluid leak, paralysis, cauda equina injury, wound dehiscence, pseudarthrosis.

‡One-, 2-, 3-, and 4-year postsurgical reoperation 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 1 additional surgery.

SPS indicates spinal stenosis; RCT, randomized controlled trial; OBS, observational; ESI, epidural steroid injection.

at 4 years (ESI −5.7 *vs.* no-ESI −11.7, $P = 0.17$). There were no significant differences in secondary outcome measures between the 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 4 years.

Crossover from assigned or chosen treatment at enrollment to final treatment is displayed in Table 5. Of the patients assigned to the surgical treatment group, 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 the nonoperative treatment group, 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) *versus* no-ESI (n = 182) cohorts, including patients who received preenrollment ESI and those who received ESI more than 3 months after enrollment in SPORT, are reported in Table 6 (Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723). At baseline, there was significantly lower incidence of patient satisfaction in the ESI cohort (ESI 71% *vs.* no-ESI 62%, $P = 0.026$). There was an increased incidence of pain radiation in the ESI cohort (ESI 82% *vs.* no-ESI 71%, $P = 0.006$), any neurological deficit (ESI 58% *vs.* no-ESI 47%, $P = 0.016$). There were higher percentages 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 PF score differences between the ESI and no-ESI groups (SF-36 PF domain or ODI). Operative details for the entire ESI cohort are reported in Table 7 (Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723). In the ESI patients, there was an increased operative time (ESI 135 min *vs.* no-ESI 115 min, $P = 0.006$) and increased length of stay (ESI 3.4 d *vs.* no-ESI 2.7 d, $P = 0.003$). Average change in outcome for all the ESI and no-ESI patients is reported in Table 8 (Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723) at each time point and in Table 9 (Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723) for aggregate area under the curve results. There was significantly less improvement in surgically treated ESI patients in SF-36 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 SF-36 BP (ESI 12.1 *vs.* no-ESI 18.8, $P = 0.004$) and SF-36 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, Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723).

DISCUSSION

These results demonstrate significantly less improvement in the ESI patients whether treated surgically or nonsurgically during the 4-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 1 or more ESIs in the initial nonoperative management of patients with spinal stenosis, these results suggest that ESI are associated with worse outcome in the treatment of spinal stenosis.

These results are in contrast to the previous ESI literature. Several previous studies have demonstrated 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, recently, Briggs *et al*[13] in a prospective observational study 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 whereas 70% of patients had recurrent symptoms and only 49% would undergo the procedure again. Additionally, 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.

TABLE 3. Total 4 Years Area Under the Curve Aggregate Change in Outcome

SPS Pre-enrollment ESI	ESI	Surgical	Nonoperative	Treatment Effect* (95% CI)
SF-36 BP (0–100), mean (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)
	P	0.053	0.007	0.36
SF-36 PF (0–100), mean (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)
	P	0.025	0.009	0.57
ODI (0–100), mean (SE)	No-ESI	−20.3 (1.2)	−10.2 (1.4)	−10.1 (−13.2 to −7)
	ESI	−16.6 (2.2)	−5.3 (2.3)	−11.3 (−15.5 to −7)
	P	0.15	0.075	0.65
Sciatica Bothersomeness Index (0–24), mean (SE)	No-ESI	−8 (0.4)	−4 (0.5)	−4.1 (−5.3 to −2.8)
	ESI	−7.2 (0.8)	−3.4 (0.8)	−3.8 (−5.5 to −2.1)
	P	0.35	0.57	0.78

SPS indicates spinal stenosis; ESI, epidural steroid injection; SF-36, 36-Item Short Form Health Survey; BP, Body Pain; PF, Physical Function, PCS, Physical Component Summary; MCS, Mental Component Summary; ODI, Oswestry Disability Index; SE, standard error.

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 drugs and home exercise. Riew *et al*[2] performed a prospective, randomized, controlled study of ESI *versus* 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, comprised patients with either spinal stenosis or lumbar disc herniation, and the data are not sufficiently specific to diagnosis to ascertain whether surgical avoidance was found only among the patients with disc herniation or spinal stenosis or only among the aggregate group. A recent update from the same investigators[16] with a minimum follow-up of 5 years found that 17 of 21 patients continued to avoid surgery, although the difference in surgical avoidance between patients treated with ESI and those treated with a local anesthetic only was no longer statistically significant. Cuckler *et al*[17] found no lasting benefit to ESI in a prospective randomized trial at an average follow-up of 20 months, classifying more than two-thirds of patients with lumbar stenosis who received ESI as treatment failures and demonstrating no benefit to receiving a second injection in cases where the first was ineffective in alleviating

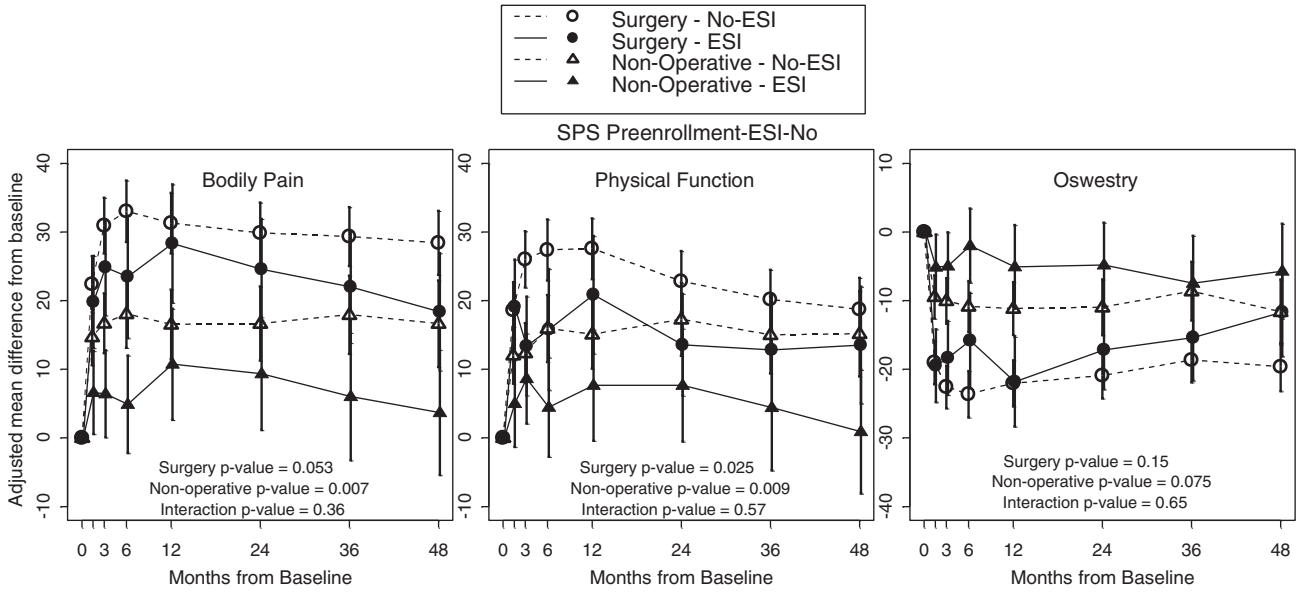

Figure 2. Change in primary outcome measures between surgically and nonsurgically treated ESI and no-ESI patients.

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 the final follow-up, both the local anesthetic and ESI groups had good or excellent results in only approximately 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 population with a single anatomical and clinical diagnosis and well-defined inclusion and exclusion criteria. Previous studies often mix patients with spinal stenosis with patients with degenerative spondylolisthesis, whereas this study excluded patients with spondylolisthesis or instability.[20,21] We included only those 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 outcome effect was observed in several different general and disease-specific outcome measures including SF-36 and Bothersomeness Index. However, this effect was not observed in ODI, a lumbar spine–specific outcome measure. Furthermore, this study compares injection *versus* noninjection as a methodology in contrast to most studies that evaluate the effect of injection *versus* placebo injection. Several previous studies have relied on administrative databases using *Current Procedural Terminology* and *International Classification of Diseases* coding, although these may not be as precise for the identification of symptomatic spinal stenosis and exclusion of patients with spondylolisthesis. This study also includes patients treated surgically and nonsurgically, and thus the study design enables estimation of the treatment effect of surgery and analysis of the results of epidural injections after surgical and nonsurgical treatment. In addition, 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 received ESI had a preference for nonsurgical treatment at baseline. Other studies that evaluate surgical avoidance associated with ESI do not include an analysis of baseline patient preference.[2] Finally, 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 that 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. ESIs have also been hypothesized to exacerbate epidural lipomatosis.[22,23] Another possible explanation is that the ESI may temporarily mask protective painful stimuli and otherwise relieve 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 a nerve injury or scarring from toxicity of the lidocaine, corticosteroid, or a carrier agent. Local anesthetics and preservatives in corticosteroids have been demonstrated to be toxic after intra-articular injections[24,25] and more recently in culture with intervertebral disc cells.[26] It is possible that subtle toxicity of the steroids[27–29] or local anesthetics directly injure neuronal[30–32] or glial elements.[33] We think 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 who chose surgery, there were increased percentages of patients who crossed over to nonsurgical treatment (ESI 33% *vs*. non-ESI 11%, $P = 0.012$). However, of the patients who were designated to undergo nonsurgical treatment, there were increased percentages of patients who elected to undergo surgical intervention (ESI 58% *vs*. no-ESI 32%, $P = 0.003$). Therefore, ESIs were associated with increased crossover both to and from surgical intervention. Because there was less improvement in the nonsurgically treated patients than in 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 the 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 were unexpected and therefore may be coincidental and unrelated to ESI. There were trends to suggest an increased incidence of multilevel and instrumented fusions in the ESI patients that we acknowledge may confound the analysis of operative time, particularly in the absence of a finding such as increased dural tear rate that may be more directly related to the ESI. The secondary analysis to exclude patients who underwent fusion did not display a statistically significant difference in operative time between groups.

There are several limitations to this study including the fact that this was a retrospective subgroup analysis that was not specified a priori. The technique of administration of epidural injections was heterogeneous, although a recent study

TABLE 4. Change Scores and Treatment Effects for Primary and Secondary Outcomes in the Randomized and Observational Cohorts of Patients With SPS Combined, According to Treatment Received*

Outcome: SPS Pre-enrollment ESI	ESI	1 yr			2 yr			3 yr			4 yr		
		Surgical	Nonoperative	Treatment Effect† (95% CI)	Surgical	Nonoperative	Treatment Effect† (95% CI)	Surgical	Nonop-erative	Treatment Effect† (95% CI)	Surgical	Nonop-erative	Treatment Effect† (95% CI)
SF-36 BP (0–100), mean (SE)‡	No-ESI	31.3 (2.3)	16.5 (2.6)	14.8 (8.4–21.1)	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)	17.6 (7–28.2)	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)
	P	0.56	0.24	0.65	0.23	0.15	0.73	0.12	0.032	0.49	0.042	0.023	0.68
SF-36 PF (0–100), mean (SE)‡	No-ESI	27.6 (2.3)	15.1 (2.6)	12.5 (6.4–18.5)	22.8 (2.3)	17.3 (2.7)	5.5 (−0.9 to 11.9)	20.2 (2.2)	15 (2.9)	5.2 (−1.4 to 11.7)	18.7 (2.4)	15.2 (3.2)	3.5 (−3.8 to 10.8)
	ESI	20.8 (4.4)	7.7 (4.1)	13.2 (3.1–23.2)	13.6 (3.8)	7.7 (4.2)	5.9 (−3.3 to 15)	12.8 (4.2)	4.4 (4.7)	8.4 (−2.3 to 19.1)	13.5 (4.3)	0.9 (4.6)	12.6 (1.8–23.4)
	P	0.19	0.13	0.91	0.037	0.059	0.95	0.12	0.055	0.61	0.29	0.011	0.17
SF-36 MCS (0–100), mean (SE)‡	No-ESI	3.7 (0.9)	0.6 (1.1)	3.1 (0.4–5.8)	2.6 (0.9)	0.5 (1.2)	2.1 (−0.8 to 4.9)	1.3 (0.9)	−0.3 (1.2)	1.6 (−1.3 to 4.6)	1.8 (1)	−0.6 (1.4)	2.3 (−1 to 5.6)
	ESI	3.6 (1.8)	3.1 (1.7)	0.5 (−4 to 5)	2.2 (1.6)	1.1 (1.8)	1.1 (−3 to 5.2)	2.9 (1.8)	2.9 (2)	0 (−5 to 4.9)	2.2 (1.9)	1 (1.9)	1.2 (−3.8 to 6.1)
	P	0.97	0.21	0.32	0.84	0.80	0.71	0.44	0.17	0.56	0.84	0.50	0.69
SF-36 PCS (0–100), mean (SE)‡	No-ESI	10.9 (0.9)	5.6 (1.1)	5.3 (2.7–7.9)	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 to 5.2)
	ESI	9.8 (1.8)	3.3 (1.7)	6.4 (2.2–10.7)	7.1 (1.6)	3.4 (1.7)	3.7 (−0.1 to 7.6)	5.3 (1.8)	1 (2)	4.3 (−0.3 to 8.9)	4.5 (1.8)	−0.2 (1.9)	4.8 (0.1–9.4)
	P	0.60	0.27	0.65	0.18	0.19	0.90	0.062	0.038	0.69	0.051	0.004	0.34
ODI (0–100), mean (SE)§	No-ESI	−22.1 (1.7)	−11.2 (2)	−10.9 (−15.6 to −6.2)	−20.9 (1.7)	−11 (2.1)	−9.9 (−14.8 to −5.1)	−18.7 (1.7)	−8.6 (2.2)	−10 (−15 to −5)	−19.7 (1.8)	−11.7 (2.4)	−8 (−13.6 to −2.4)
	ESI	−21.8 (3.3)	−5.1 (3.1)	−16.7 (−24.5 to −9)	−17.2 (2.9)	−4.8 (3.2)	−12.4 (−19.5 to −5.3)	−15.4 (3.2)	−7.5 (3.5)	−7.9 (−16.1 to 0.3)	−11.7 (3.3)	−5.7 (3.5)	−6 (−14.3 to 2.4)
	P	0.95	0.10	0.21	0.27	0.11	0.57	0.37	0.78	0.66	0.033	0.17	0.69
Sciatica Bothersomeness Index (0–24), mean (SE)¶	No-ESI	−9.4 (0.6)	−4.1 (0.7)	−5.4 (−7.1 to −3.6)	−8.6 (0.6)	−4.7 (0.7)	−3.9 (−5.7 to −2)	−8.3 (0.6)	−4.7 (0.8)	−3.6 (−5.5 to −1.7)	−8.8 (0.7)	−4.3 (0.9)	−4.6 (−6.7 to −2.5)
	ESI	−8.9 (1.2)	−3.2 (1.1)	−5.7 (−8.5 to −2.9)	−7.3 (1)	−3.7 (1.2)	−3.6 (−6.3 to −1)	−9.1 (1.2)	−5.1 (1.3)	−3.9 (−7.1 to −0.8)	−5.8 (1.2)	−3.8 (1.3)	−2.1 (−5.3 to 1.1)
	P	0.67	0.49	0.84	0.27	0.46	0.87	0.56	0.79	0.84	0.032	0.75	0.19

(*Continued*)

TABLE 4. (*Continued*)

Outcome: SPS Pre-enrollment ESI	ESI	1 yr			2 yr			3 yr			4 yr		
		Surgical	Nonoperative	Treatment Effect† (95% CI)	Surgical	Nonoperative	Treatment Effect† (95% CI)	Surgical	Nonoperative	Treatment Effect† (95% CI)	Surgical	Nonoperative	Treatment Effect† (95% CI)
Low Back Pain Bothersomeness Scale (0–6), mean (SE)‖	No-ESI	−2.1 (0.2)	−1.1 (0.2)	−1 (−1.5 to −0.5)	−2.1 (0.2)	−1 (0.2)	−1.1 (−1.6 to −0.6)	−2 (0.2)	−1 (0.2)	−1 (−1.5 to −0.5)	−1.8 (0.2)	−1 (0.2)	−0.8 (−1.4 to −0.2)
	ESI	−2.3 (0.3)	−1.1 (0.3)	−1.2 (−2 to −0.4)	−1.9 (0.3)	−1.1 (0.3)	−0.8 (−1.6 to 0)	−2.2 (0.3)	−1.2 (0.4)	−1 (−1.9 to −0.1)	−1.3 (0.3)	−1.3 (0.3)	0 (−0.9 to 0.9)
	P	0.62	0.82	0.60	0.49	0.88	0.56	0.67	0.75	0.99	0.20	0.49	0.17
Very/somewhat satisfied with symptoms (%)	No-ESI	73.7	25.8	47.9 (33.9–61.9)	77.7	26	51.7 (37.4–66)	70.6	36.1	34.4 (17.8–51.1)	70.9	37.5	33.4 (14.8–52)
	ESI	67.1	25.2	42 (16.9–67)	52.9	36.2	16.7 (−8.5 to 41.9)	64.4	48.3	16.1 (−13.8 to 45.9)	41.9	22.2	19.8 (−6.5 to 46)
	P	0.58	0.95	0.72	0.012	0.37	0.009	0.57	0.37	0.27	0.019	0.25	0.56

**Adjusted for center, age, sex, baseline score, income, treatment preference, duration of symptoms, compensation, smoking status, body mass index, baseline Sciatica Bothersomeness Index, and joint, stomach, and bowel problems.*

†Treatment effect is the difference between the surgical and nonoperative mean change from baseline. The analysis is done using a mixed model with a random subject intercept term. Treatment is a time-varying covariate where a patient's experience prior to surgery is attributed to the nonoperative arm and time is measured from enrollment, and his or her postsurgery outcomes are attributed to the surgical arm and time is measured from the time of surgery.

‡SF-36 scores range from 0 to 100, with higher score indicating less severe symptoms.

§The ODI 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 ranges from 0 to 6, with lower scores indicating less severe symptoms

SPS indicates spinal stenosis; ESI, epidural steroid injection; SF-36, 36-Item Short Form Health Survey; BP, body pain; PF, physical function, PCS, Physical Component Summary; MCS, Mental Component Summary; ODI, Oswestry Disability Index; SE, standard error.

TABLE 5. Crossover of Assigned/Chosen Treatment Groups at 4 Years' Follow-up Interval for the Patients With SPS Without Pre-enrollment ESI

SPS Pre-enrollment ESI	No-ESI (n = 207)	ESI (n = 69)	*P**
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 χ^2 test, where there is a statistically significant difference in crossover between the ESI and no-ESI groups for the surgical and nonoperative groups, respectively.*

SPS indicates spinal stenosis; ESI, epidural steroid injection.

suggests that there are no significant differences in outcome based on the ESI technique.[34] Furthermore, we do not have information on whether the injections were fluoroscopically guided or the nature of the corticosteroid administered (particulate *vs*. nonparticulate). 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 toward no difference in outcome, not less improvement. There are other limitations that are common to subgroup analyses of prospective randomized studies.[8] Because patients were not randomized to epidural *versus* no-epidural treatment, there is the possibility of an unknown confounder biasing the results. Although the known common confounding variables (age, workers compensation status, duration of symptoms, obesity, smoking, *etc*.) were not statistically significantly different between groups (Table 1), we acknowledge that an unknown confounder possibly unrelated to the ESIs (such as sagittal imbalance) may have influenced results and produced a type 1 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 ESI was a statistically significant preference for nonsurgical treatment at baseline in the ESI patients. It is possible that this baseline preference may reflect a risk aversion behavior that may confound the outcome of surgical and nonsurgical treatment.

Another possible confounder is the limitation of the study population to patients who received epidural injections within 3 months. This decision was made prior to review of the data to exclude patients who received epidural injections as a salvage intervention after a failed attempt at nonsurgical treatment late in the study. Similarly, patients who had received ESI prior to enrollment were also excluded because of 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 (Supplemental Digital Content 2, available at http://links.lww.com/BRS/A723). 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 cohort of ESI patients had statistically significantly less improvement in pain during the study period. Because the difference in outcome was also observed in the larger group of patients who received epidurals during the SPORT study period as well as the initial study cohort (3 mo), 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 suggest that an intrinsic property of the ESI is likely causative because 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.

➢ Key Points

- ❑ The study evaluated whether patients with spinal stenosis who received ESI had improved outcome and surgical avoidance compared with patients who did not receive ESI.
- ❑ ESIs were associated with significantly less improvement at 4 years among all patients with spinal stenosis in SPORT.
- ❑ Of the surgically treated patients, ESIs were associated with longer duration of surgery and longer hospital stay. ESIs were not associated with long-term surgical avoidance.

Supplemental digital content is available for this article. Direct URL citations appearing in the printed text are provided in the HTML and PDF version of this article on the journal's web site (www.spinejournal.com).

References

1. Lebude B, Wang D, Harrop JS, et al. Clinical survey: patterns of utilization of lumbar epidural steroid injections by a cohort of spinal surgeons. *PM R* 2009;1:329–34.
2. Riew KD, Yin Y, Gilula L, et al. The effect of nerve-root injections on the need for operative treatment of lumbar radicular pain. A prospective, randomized, controlled, double-blind study. *J Bone Joint Surg Am* 2000;82-A:1589–93.
3. Sayegh FE, Kenanidis EI, Papavasiliou KA, et al. Efficacy of steroid and nonsteroid caudal epidural injections for low back pain and sciatica: a prospective, randomized, double-blind clinical trial. *Spine (Phila Pa 1976)* 2009;34:1441–7.
4. Staal JB, de Bie RA, de Vet HC, et al. Injection therapy for subacute and chronic low back pain: an updated Cochrane review. *Spine (Phila Pa 1976)* 2009;34:49–59.

5. Price C, Arden N, Coglan L, et al. Cost-effectiveness and safety of epidural steroids in the management of sciatica. *Health Technol Assess* 2005;9:1–58, iii.
6. Birkmeyer NJ, Weinstein JN, Tosteson AN, et al. Design of the Spine Patient Outcomes Research Trial (SPORT). *Spine (Phila Pa 1976)* 2002;27:1361–72.
7. Weinstein JN, Tosteson TD, Lurie JD, et al. Surgical versus nonoperative treatment for lumbar spinal stenosis four-year results of the spine patient outcomes research trial. *Spine (Phila Pa 1976)* 2010;35:1329–38.
8. Sun X, Briel M, Walter SD, et al. Is a subgroup effect believable? Updating criteria to evaluate the credibility of subgroup analyses. *BMJ* 2010;340:c117.
9. Brazier JE, Harper R, Jones NM, et al. Validating the SF-36 Health Survey Questionnaire: new outcome measure for primary care. *BMJ* 1992;305:160–4.
10. Garratt AM, Ruta DA, Abdalla MI, et al. The SF36 Health Survey Questionnaire: an outcome measure suitable for routine use within the NHS? *BMJ* 1993;306:1440–4.
11. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)* 2000;25:2940–52; discussion 2952.
12. Patrick DL, Deyo RA, Atlas SJ, et al. Assessing health-related quality of life in patients with sciatica. *Spine (Phila Pa 1976)* 1995;20:1899–908; discussion 1909.
13. Briggs VG, Li W, Kaplan MS, et al. Injection treatment and back pain associated with degenerative lumbar spinal stenosis in older adults. *Pain Phys* 2010;13:E347–55.
14. Lee JW, Myung JS, Park KW, et al. Fluoroscopically guided caudal epidural steroid injection for management of degenerative lumbar spinal stenosis: short-term and long-term results. *Skeletal Radiol* 2010;39:691–9.
15. Koc Z, Ozcakir S, Sivrioglu K, et al. Effectiveness of physical therapy and epidural steroid injections in lumbar spinal stenosis. *Spine (Phila Pa 1976)* 2009;34:985–9.
16. Riew KD, Park JB, Cho YS, et al. Nerve root blocks in the treatment of lumbar radicular pain. A minimum five-year follow-up. *J Bone Joint Surg Am* 2006;88:1722–5.
17. Cuckler JM, Bernini PA, Wiesel SW, et al. The use of epidural steroids in the treatment of lumbar radicular pain. A prospective, randomized, double-blind study. *J Bone Joint Surg Am* 1985;67:63–6.
18. Fukusaki M, Kobayashi I, Hara T, et al. Symptoms of spinal stenosis do not improve after epidural steroid injection. *Clin J Pain* 1998;14:148–51.
19. Friedly J, Nishio I, Bishop MJ, et al. The relationship between repeated epidural steroid injections and subsequent opioid use and lumbar surgery. *Arch Phys Med Rehabil* 2008;89:1011–5.
20. Atlas SJ, Keller RB, Wu YA, et al. Long-term outcomes of surgical and nonsurgical management of lumbar spinal stenosis: 8 to 10 year results from the Maine Lumbar Spine Study. *Spine (Phila Pa 1976)* 2005;30:936–43.
21. Slatis P, Malmivaara A, Heliovaara M, et al. Long-term results of surgery for lumbar spinal stenosis: a randomised controlled trial. *Eur Spine J* 2011;20:1174–81.
22. Tok CH, Kaur S, Gangi A. Symptomatic spinal epidural lipomatosis after a single local epidural steroid injection. *Cardiovasc Intervent Radiol* 2011;34(suppl 2):S250–5.
23. Danielson KD, Harrast MA. Focal spinal epidural lipomatosis after a single epidural steroid injection. *PM R* 2011;3:590–3.
24. Piper SL, Kim HT. Comparison of ropivacaine and bupivacaine toxicity in human articular chondrocytes. *J Bone Joint Surg Am* 2008;90:986–91.
25. Grishko V, Xu M, Wilson G, et al. Apoptosis and mitochondrial dysfunction in human chondrocytes following exposure to lidocaine, bupivacaine, and ropivacaine. *J Bone Joint Surg Am* 2010;92:609–18.
26. Ren J, Zhang Y, Chee A, et al. Effects of local anesthetic and nonionic contrast agents on bovine intervertebral disc cells cultured in alginate. Paper presented at: North American Spine Society Annual Meeting; October 6, 2010; Chicago, IL. Available at: http://www.nassannualmeeting.org/Documents/am10_finalprogram.pdf. Accessed October 5–9.
27. Aden P, Goverud I, Liestol K, et al. Low-potency glucocorticoid hydrocortisone has similar neurotoxic effects as high-potency glucocorticoid dexamethasone on neurons in the immature chicken cerebellum. *Brain Res* 2008;1236:39–48.
28. Dani C, Vestri V, Bertini G, et al. Toxicity of corticosteroids and catecholamines for mice neuronal cell cultures: role of preservatives. *J Matern Fetal Neonatal Med* 2007;20:325–33.
29. Wang PH, Tsai CL, Lee JS, et al. Effects of topical corticosteroids on the sciatic nerve: an experimental study to adduce the safety in treating carpal tunnel syndrome. *J Hand Surg Eur Vol* 2011;36:236–43.
30. Perez-Castro R, Patel S, Garavito-Aguilar ZV, et al. Cytotoxicity of local anesthetics in human neuronal cells. *Anesth Analg* 2009;108:997–1007.
31. Friederich P, Schmitz TP. Lidocaine-induced cell death in a human model of neuronal apoptosis. *Eur J Anaesthesiol* 2002;19:564–70.
32. Werdehausen R, Braun S, Essmann F, et al. Lidocaine induces apoptosis via the mitochondrial pathway independently of death receptor signaling. *Anesthesiology* 2007;107:136–43.
33. Yang S, Abrahams MS, Hurn PD, et al. Local anesthetic Schwann cell toxicity is time and concentration dependent. *Reg Anesth Pain Med* 2011;36:444–51.
34. Smith CC, Booker T, Schaufele MK, et al. Interlaminar versus transforaminal epidural steroid injections for the treatment of symptomatic lumbar spinal stenosis. *Pain Med* 2010;11:1511–5.