

**Radcliff K, Kepler C, et al. Epidural Steroid Injections Are Associated With Less Improvement in Patients With Lumbar Spinal Stenosis. A Subgroup Analysis of the Spine Patient Outcomes Research Trial. Spine 2013;38:279-291.**

Design: Subgroup analysis of a combined randomized and observational clinical trial

Population/sample size/setting:

- 276 patients (96 women, 180 men, mean age 65) who were a subgroup of the SPORT study of lumbar spinal stenosis (original combined cohort had n=634)
- The purpose of the study was to compare patients who had and did not have ESI within the first 3 months of enrollment in SPORT, reducing the study population from 634 to 276
- Eligibility and exclusion criteria for SPORT were as reported in Weinstein 2008 reviewed elsewhere
- Patients were divided into groups according to the timing of ESI during the SPORT study
  - o Those who had received ESI within the first three months of enrollment in SPORT were included; those who had ESI at enrollment or later than 3 months after enrollment were excluded
  - o These exclusions were done to avoid biases arising from patients who had already failed on ESI at enrollment and biases arising from using ESI as a salvage procedure after the failure of other interventions

Comparisons and outcomes:

- Patients who had ESI in the first 3 months (n=69) were compared with those who did not receive any ESI during SPORT (n=207)
- Main outcome measures were pain and function, measured by the Bodily Pain (BP) and the Physical Function (PF) subscales of the SF-36, and by the Oswestry disability index
  - o These were measured 6 weeks, 3 months, 6 months, and yearly up to 4 years after enrollment
  - o Secondary measures included the Stenosis Bothersomeness Index, the Low Back Pain Bothersomeness Scale, and the Leg Pain Bothersomeness Scale, measured at the same time points as the primary outcome measures
- At baseline, the ESI and no-ESI groups did not differ in the primary outcome measures, but the ESI group did have an increased preference for nonsurgical treatment (62%) compared to the no-ESI group (33%)
- During the 4 years of SPORT, most of the study patients had operative treatment (ESI, n=41; no-ESI, n=134)
  - o The groups had similar frequencies of the different procedures (decompression vs fusion, multilevel fusion, laminectomy level, or number of levels decompressed)
  - o There were significant differences that favored the no-ESI group; length of hospital stay and operative time were both shorter for the group with no ESI

- Comparisons of outcome measures were done with SAS PROC MIXED, which is adapted for comparing groups at multiple longitudinal time intervals
- Comparisons were adjusted for potential confounders: age, sex, marital status, smoking, race, compensation, herniation, location, work status, baseline symptom scores, and symptom duration
- The group comparisons were done separately for surgically treated and non-surgically treated patients, first in a comparison not adjusted for the potential confounders:
  - o Averaged over 4 years, there was significantly less improvement among the surgically treated ESI patients than in non-ESI on SF-36 PF and a trend towards less improvement on the SF-36 BP score
  - o Averaged over 4 years, there was significantly less improvement in the non-surgically treated ESI for both the SF-36 PF and the SF-36 BP scores
  - o In both groups, there was a trend for less improvement in the Oswestry scores in the ESI group, but this did not reach statistical significance
- When the comparisons were repeated with adjustment for multiple confounders, the disadvantage of the ESI versus the no-ESI groups persisted
  - o The surgically treated ESI group did less well than the no-ESI group on the SF-36 BP and Oswestry scores averaged over 4 years
  - o The nonsurgically treated EIS group also had less improvement over 4 years on the SF-36 bp and PF subscales
- In all of the randomized cohorts of the three major SPORT studies (herniated disc, degenerative spondylolisthesis, and spinal stenosis), there was considerable crossover from allocated treatments and treatments actually received, both from operative to nonoperative treatment and vice versa
  - o In the spinal stenosis trial, crossovers from surgical assignment to nonoperative treatment was more frequent in those who had ESI (33%) versus those who had no ESI (11%)
  - o In the opposite direction from nonoperative assignment to surgical treatment, there was increased crossover to surgical treatment in the patients who had ESI (58%) than in those with no ESI (32%)
- Several additional analyses were done on the entire SPORT spinal stenosis cohort, including those who had ESI either at enrollment or more than 3 months after enrollment; these were reported in a separate online document and were not part of the printed text
  - o It was seen that most of the entire SPORT population had ESI (n=452) versus no ESI (n=182)
  - o In contrast to the 276 patients in the subgroup analysis, the ESI patients for the entire SPORT cohort had less favorable baseline scores on several pertinent measures, including pain radiation and neurologic deficits
  - o These contrasts underscore the importance of confining the subgroup analysis to those patients whose ESI occurred in the first 3 months after enrollment in SPORT

Authors' conclusions:

- Patients with spinal stenosis who had ESI had significantly less improvement than those who did not receive ESI
  - An intrinsic property of ESI (mass effect, subtle toxicity of steroid or local anesthetic, increased adhesions or scarring) is likely causative because this effect was seen in both surgical and nonsurgical patients
  - However, it is possible that an unmeasured (and therefore unadjusted) confounder may account for the group differences between ESI and no ESI
  - There may have been some technical heterogeneity (fluoroscopy, translaminar/transforaminal injection, particulate/nonparticulate steroid), but such heterogeneity would be expected to bias the results toward the null hypothesis rather than bias them in the direction of harm from ESI

Comments:

- Most of the criteria for a good observational study are met: exposure (ESI) is unequivocally measured, the outcomes are based on well-validated scales, numerous confounders are controlled for, and follow-up is both short and long term
- Not all of the contrasts are great in magnitude, and several are reported as “trends” (when  $p > 0.05$ )
- The crossovers do not have a clear interpretation, since the study has combined participants from both the randomized and observational cohorts of the original SPORT population; participants who changed their initial preference are mixed with those who consented to be randomized and later crossed over to the treatment to which they were not randomized
  - o Table 5 points to no clear direction regarding the effect of ESI on surgical avoidance; the first row makes it appear that ESI enabled surgical patients to cross over to nonoperative treatment, but the second row makes it appear that ESI led to nonsurgical patients crossing over to surgery
- There may be one or more manuscript errors: Tables 1 and 2 are headed “Pre-enrollment ESI” even though such patients were excluded from the analysis
  - o Also, at the start of the Results section, it is stated that there were 154 patients who had ESI within 3 months of enrollment, immediately after this number is reported as 69
  - o The number 154 happens to be exactly equal to the number of patients who received ESI in the first three months of the SPORT study on herniated discs
  - o The author has been e-mailed with inquiries on these two points for clarification, and confirms that the headings for the tables should read “No pre-enrollment ESI”
  - o The author confirms also that the correct number of ESI in the first 3 months is 69
- It remains possible that the patients who had ESI also had other characteristics associated with less favorable prognosis at baseline; the authors' hypothesis of

a causal connection with ESI and less favorable outcomes is not clearly proved

- However, the data do conflict with any hypothesis that ESI is a useful treatment for LSS, and provide grounds for deferring those injections when spinal stenosis is present
  - o Although it is not discussed by the authors, the biology of symptoms in spinal stenosis is more likely to involve a transient ischemic mechanism rather than an inflammatory mechanism
  - o If a positional ischemic neuropathy is an important mechanism of neurogenic claudication, a trial of steroid injection could delay a decompressive intervention and could be a disservice to the patient
- The route of administration is not reported, and in the SPORT trial there is not enough information to determine whether the interlaminar/transforaminal administration had different effects
  - o The authors cite a 2010 article (Smith et al) which reports that neither route of administration produces superior results in the setting of LSS

Assessment: Adequate for some evidence that epidural steroids are unlikely to be beneficial in the setting of spinal stenosis; not adequate for evidence that steroid injections have a direct detrimental effect, but may unnecessarily delay surgical decompression, which is supported by good evidence elsewhere

#### References:

Smith CG, Booker T. Interlaminar versus Transforaminal Epidural Steroid Injections for the Treatment of Symptomatic Lumbar Spinal Stenosis. Pain Medicine 2010;11:1511-1515.

Weinstein JN, Tosteson TD, et al. Surgical versus Nonsurgical Treatment for Lumbar Spinal Stenosis. N Engl J Med 2008;358:794-810.