Pinto RZ, Maher CG, et al. Epidural Corticosteroid Injections in the Management of Sciatica: A Systematic Review and Meta-analysis. Ann Intern Med 2012;157:865-877.

Design: Meta-analysis of randomized clinical trials

PICOS:

- Patient population: Patients with sciatica defined as pain radiating below the knee, designated as radiculopathy, nerve root compromise, nerve root compression, lumbosacral radicular syndrome, disc herniation, radiculitis, nerve root pain, or nerve root entrapment
    - 3 levels of duration were considered for the analysis: acute (<6 weeks), subacute (6-12 weeks), and chronic (>12 weeks)
    - Trials reporting inclusion of patients with previous back surgery or spinal canal stenosis were excluded; studies of foraminal or lateral recess stenosis were included
- Intervention: Epidural corticosteroid injections (ESI)
- Comparison intervention: Similar placebo interventions, including injections in which both groups received an epidural injection of a short-duration local anesthetic
- Outcomes: Overall pain intensity, leg pain, back pain, and disability
    - Meta-analysis focused on studies reporting outcomes on a continuous scale, such as the Visual Analog Scale or the Numerical Rating Scale for pain, and on the Oswestry or Roland-Morris scales for disability
    - To permit calculation of a weighted mean difference between treatment groups, all outcomes were converted to a scale of 0-100
    - Studies reporting results as percentages of "improved" patients were included in the systematic review but were excluded from the meta-analysis, since the definition of "improved" varied between studies
    - Estimates of treatment effects were ranked in hierarchical order: mean differences adjusted for covariates including baseline scores; changes in pain/disability scores not adjusted for other covariates; final pain/disability values (which do not take baseline scores into account)
- Study types: Randomized controlled trials of ESI administered by one of three routes: caudal, transforaminal, or translaminar, comparing each with a placebo

Study selection:

- Databases were MEDLINE, EMBASE, International Pharmaceutical Abstracts, CINAHL, and the Cochrane Register of Controlled Trials
- Hand searches were done of the references of eligible clinical trials
- Only studies published in English were included
- Data extraction was done by 2 reviewers, who assessed the quality of the studies using the Physiotherapy Evidence Database (PEDro) Scale
    - PEDro is similar to the Cochrane method for assessing risk of bias: random allocation with concealment of the allocation list, blinding,

analysis by intention-to-treat, and adequate follow-up; the Cochrane evaluation also includes assessment of selective outcome reporting

- Levels of evidence were ranked using GRADE (Grading of Recommendations Assessment, Development, and Evaluation)
    - High quality: further research is very unlikely to change confidence in estimate of effect
    - Moderate quality: further research is likely to have an important effect on confidence in the estimate of effect and may change the estimate
    - Low quality: further research is very likely to have an important effect on confidence of the estimate of effect and is likely to change the estimate)
    - Very low quality: we are very uncertain about the estimate

Results:

- 1490 potentially relevant citations were retrieved from the search databases; 114 were retrieved for evaluation of the full text; and 23 trials were included in the review
- There were 6 trials of the transforaminal route, 4 trials of the caudal approach, and 13 trials of the translaminar route
- There were some risks of bias in most of the studies; 15 of the 23 studies failed either to conceal the allocation list, perform intension-to-treat analysis, or blind the injector of the steroid or placebo preparation
- There was no evidence of publication bias or serious small study effects; this meant that the quality of the meta-analyses did not need to be downgraded due to the problem of disproportionate publication of studies with positive results
- For short-term effects, there were data for leg pain, back pain, and disability, and the overall quality of the evidence was high:
    - Leg pain data was available for 1316 patients in 14 trials; there was a statistically significant but clinically unimportant effect of ESI over placebo (only 6.2 points on a scale of 0 to 100)
    - Back pain data was available for 723 patients in 6 trials; there was no effect of ESI over placebo
    - Disability data was available for 1154 patients in 10 trials; there was a statistically significant but clinically unimportant effect of ESI over placebo (3.1 points on a scale of 0 to 100)
- For long-term effects, there were data for leg pain, back pain, and disability; again, the overall quality of the evidence was high:
    - For all three outcomes, the effects of ESI over placebo was clinically unimportant and statistically nonsignificant; this included data for leg pain (714 patients in 7 trials), back pain (453 patients in 3 trials), and disability (691 patients in 6 trials)
- The meta-analyses were statistically homogeneous when analyses were done for potentially clinically heterogenous studies
    - The route of administration of ESI made no difference; the generally accepted measure of heterogeneity (I^2) has a lower threshold of 25%,

and for short-term followup of leg pain, this measure was 10%; for long-term followup, it was 15%

Authors' conclusions:

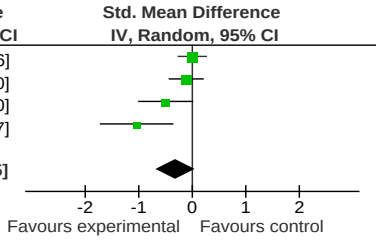
- There is high quality evidence that ESI has small short-term effects on leg pain and disability in patients with sciatica, but these effects are below the thresholds for any clinically important change in pain and disability (10 to 30 points on a 100 point scale)
- There is high quality evidence that ESI has no long-term effects on leg pain or disability
- There is high quality evidence that ESI has no effect on back pain in either the short or long term
- There was not enough information to allow an estimate of the safety of adverse effects of ESI from the trials in the study
- Patients with sciatica should receive a course of noninvasive care before any kind of invasive care is considered

Comments:

- The percentage of patients with 50% reduction in pain is a commonly measured outcome of "success" in the chronic pain literature, but was not considered by the authors because of differences in the definitions of success in the available studies
    - Mean differences between groups may sometimes obscure true treatment effects in subgroups of patients, due to the fact that the distribution of pain responses may not be normally distributed
    - It still appears unlikely that any true differences between ESI and placebo were badly obscured by the method of analysis chosen by the authors
- The clinical and statistical homogeneity of the meta-analyses was noteworthy; specifically, the lack of a difference between caudal, transforaminal, and translaminar approaches was somewhat unexpected
- The authors used a random effects model for their meta-analyses, even though the homogeneity of the studies could have justified a fixed-effect model; the difference between the two models is not important in this setting
- "High quality evidence" reflects the authors' opinion that future research is not likely to change the estimate of the effect of ESI on sciatica, and corresponds to "strong" evidence in the general principles of the WC guidelines
- In some of the studies, the volumes of injectate were different, with the corticosteroid group receiving a larger volume of injectate than the placebo group:

Study or Subgroup	Steroid Mean	Steroid SD	Steroid Total	Placebo Mean	Placebo SD	Placebo Total	Weight	Std. Mean Difference IV, Random, 95% CI
Arden 2005	-15	32	120	-15	32	108	31.9%	0.00 [-0.26, 0.26]
Carette 1997	-26.5	36	77	-22.5	34.4	79	29.6%	-0.11 [-0.43, 0.20]
Ghahreman 2010	41	30	28	55	26	37	22.1%	-0.50 [-1.00, 0.00]
Helliwell 1985	-25	20	20	-7	13	19	16.4%	-1.04 [-1.71, -0.37]
Total (95% CI)			**245**			**243**	**100.0%**	**-0.31 [-0.67, 0.05]**

Heterogeneity: Tau² = 0.09; Chi² = 9.83, df = 3 (P = 0.02); I² = 69%
Test for overall effect: Z = 1.71 (P = 0.09)



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- Since volume of injectate has been suggested (Rabinovitch 2009) as a variable influencing the effectiveness of ESI (possibly a lavage effect), it could be noted that Arden 2005, which used 10 ml in the steroid group and 2 ml in the saline group, reported an effect size of zero, and that the pooled standardized mean difference falls short of statistical significance
- Studies published after 2000, in general, reported smaller effects of ESI than studies published earlier than 2000; all included transforaminal studies were published after 2000
- All transforaminal injections were done with fluoroscopic guidance; among the studies of the interlaminar approach, only Manchikanti 2010 used fluoroscopy, and had results on short-term leg pain and on disability which were not statistically significant
    - Fluoroscopic guidance does not appear to lead to clinically important treatment effect sizes
    - There were three studies of caudal ESI; the only one which was “statistically significant” in favor of ESI was the one which did not mention guidance of the injection; of the other two, one used ultrasound and the other used fluoroscopy, and they did not show an ESI effect
- Separate analysis of short term leg pain with transforaminal ESI which used a saline placebo as the control group cannot be done with Cochrane software, but can be done in Excel; a standardized mean difference for these three studies (Cohen, Karppinen, and Ghahreman) is 0.235; with a pooled standard deviation of about 32.25, this is a weighted mean difference of only 7.6 points on a 100 point scale; there is little difference between a saline and a local anesthetic placebo, even though this is a plausible subgroup to analyze
- In summary, subgroup analyses of differing injectate volumes, presence or absence of imaging guidance, and saline versus local anesthetic control groups, do not demonstrate that these lead to different estimates of the effect of ESI on short term leg pain
- Subgroup analyses of some potentially relevant patient characteristics (factors that exacerbate pain, details of pain pattern) are not testable
    - However, selection criteria were not uniform across all studies
    - For example, Karppinen 2001 and Ghahreman 2010 had different effect sizes, and also had different inclusion criteria
    - Karppinen had a small (Cohen’s d=0.25) and statistically nonsignificant effect size
    - Ghahreman had a moderate (Cohen’s d=0.5) and statistically significant (95% confidence interval for d between 1 and 0) effect size

    - Ghahreman had more stringent inclusion criteria than Karppinen; Ghahreman required that the radiating pain be lancinating, burning, stabbing or electric in nature and excluded patients with only deep aching pain which could be indicative of somatic referred pain; straight leg raising was also a required criterion for entry
    - Karppinen included patients with dermatomally radiating pain and did not specify its quality; also, straight leg raising was not required
    - These contrasts suggest avenues for later exploration, but no firm conclusions can be drawn from the contrasts
- The authors' conclusions apply to average pain responses among all patients with sciatica, and do not necessarily imply that no patients experience benefit from the procedure (in the positive tails of the pain response distribution)
    - However, a corollary of this is that some patients may experience harm from the procedure (in the negative tails of the same distribution)
    - Measures of central tendency, such as means and standard deviations, may not adequately represent situations in which there is a bimodal distribution of effects, such as two subgroups with different responses to an intervention

Assessment: High quality meta-analysis justifying strong evidence that ESI does not, on average, provide clinically meaningful improvements in leg pain, back pain, or disability in patients with sciatica (radicular lumbar pain/radiculopathy). Strong evidence that ESI has a small average short term benefit for leg pain and disability in patients with sciatica. Strong evidence that ESI has no short or long term benefit for back pain.

Referenced studies:

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Additional references:

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