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A Multi-Center, Randomized, Double-Blind, Comparative-Efficacy Study Comparing Epidural Steroid Injections to Gabapentin for Neuropathic Low Back Pain

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Abstract

Objective: To evaluate whether ESI or gabapentin is a better treatment for lumbosacral radiculopathy.

Design: A multicenter randomized study was conducted between 2011 and 2014. Computer-generated randomization was stratified by site. Patients and evaluating physicians were blinded to treatment outcomes.

Settings: Eight military, Veterans Administration and civilian hospitals.

Participants: 145 subjects with neuropathic low back pain secondary to herniated disc or spinal stenosis < 4 years in duration, and leg ≥ back pain.

Interventions: Participants received either ESI + placebo pills or sham ESI + gabapentin.

Main outcome measure: Average leg pain 1 month after the injection. All patients had 1-month follow-up visits; patients whose condition improved remained blinded for their 3-month visit.

Results: No significant differences were noted for the primary outcome measure (mean change from baseline -2.2 ± 2.4 in the ESI group vs. -1.7 ± 2.6 in the gabapentin group; p=0.174). 1-month after treatment those who received ESI had greater reductions in worst leg pain (-3.0 ± 2.8) than those treated with gabapentin (-2.0 ± 2.9; p=0.026) and were more likely to experience a positive successful outcome (67.6% vs. 47.2%; p=0.014). At 3-months, no significant differences were noted between treatments except that a higher percentage of ESI subjects experienced a positive global perceived effect (51.6% vs. 33.8%; p=0.037).

Conclusions: Although ESI may provide greater benefit for some outcome measures than gabapentin, the differences are small and for most people transient. Treatment decisions should be based on patient considerations, rather than differences in efficacy.

Trial registration: ClinicalTrials.gov Identifier: NCT01495923

Introduction

The physical, socioeconomic and psychological impact of low back pain (LBP) is enormous. LBP has been the leading cause of years lost to disability over the past several decades,[1] with a lifetime prevalence that ranges between 50% and 90%.[2,3] The economic cost is estimated to exceed $100 billion per year in the U.S, over half of which can be attributed to lost productivity.[3,4] Efforts to address the worldwide burden posed by LBP amount to an international crisis.

The classification of back pain is perhaps the most important distinction for clinicians to make, as it informs work-up and treatment decisions at all levels of care.[5] Since the development of validated instruments to categorize LBP,[6,7] studies have determined that the proportion of chronic LBP cases that are predominantly neuropathic (e.g. radicular pain from a herniated disc or neurogenic claudication from spinal stenosis) ranges between 17% and 55%,[7-11] with one review finding a median prevalence rate of 41%.[12] Whereas the presence of neuropathic symptoms portends a more negative prognosis for acute LBP episodes,[13] chronic neuropathic LBP may be more responsive to procedural interventions than non-specific back pain.[12,14]

Epidural steroid injections (ESI) are the most commonly performed pain procedure in the world,[15] being more frequently utilized and effective for neuropathic than mechanical spine pain.[12,16] Although mixed, most controlled studies have also found pharmacotherapy with gabapentinoids to be somewhat effective for chronic neuropathic LBP.[17-21]

Numerous controlled trials have been performed evaluating ESI and medications in LBP, with review articles generally reporting modest effects.[12, 22] Yet, for clinicians the more relevant

question is not whether a real treatment is better than a sham treatment, but which treatment is more effective.[23]

Several small, randomized, open-label studies have compared ESI to medications. One study showed superiority for a single ESI at one month but not later follow-up compared to tramadol and a muscle relaxant.[24] A second demonstrated that a single caudal ESI provided better pain relief than non-steroidal anti-inflammatory drugs through 3 months.[25] However, neither study evaluated first-line adjuvants (e.g. gabapentin) as a comparison group. A more recent, 3-armed multi-center study performed in 169 patients with cervical radiculopathy compared a series of ESI, to gabapentin and/or nortriptyline plus physical therapy, to a combination group that received both injections and conservative care, and found that the combination group experienced a higher success rate at 3 but not 6 months.[26] Although these studies may simulate real-life decisions facing clinicians, the fact that none were blinded precludes any conclusions regarding efficacy. The purpose of our study is to compare a single ESI to gabapentin in patients with neuropathic LBP in a double-blinded fashion.

Methods

We performed a double-blind, randomized study comparing a single ESI to gabapentin. Approval to conduct this study was granted by the Internal Review Boards at all 8 participating institutions, and all subjects who provided informed consent. All participants were treated between December 2011 and June 2014.

Participants & Settings

The study sites consisted of 4 joint service military treatment facilities, 3 of which serve as teaching hospitals (Walter Reed, San Diego and San Antonio) and one of which is located in Europe; a VA hospital and 3 civilian teaching hospitals (Johns Hopkins, Case Western and Penn State). Inclusion criteria were age $\geq$ 18 years; average leg pain score $\geq$ 4 on a 0- 10 numerical rating scale (NRS) scale over the preceding week, or $\geq$ 3/10 if greater or equal to back pain; duration of current symptoms > 6 weeks and $\leq$ 4 years; and signs and/ or symptoms of lumbosacral radicular pain or neurogenic claudication with concordant magnetic resonance imaging. Exclusion criteria were neuropathic pain > 4 years in duration; previous failed trial with or adverse reaction to gabapentin or pregabalin; ESI within the past 3 years; cauda equina syndrome; previous spine surgery; pregnancy; allergic reaction to contrast dye; and serious medical or psychiatric condition that might preclude an optimal response to treatment.

Randomization and Interventions

145 participants were randomized in a 1:1 ratio by computer-generated randomization tables. Enrollment was done by an investigator physician. Allocation was performed in groups of 36 (Walter Reed and Johns Hopkins) or 18 by research nurses, with treatment divulged via a sealed envelope prior to injection. Participants at each site were sub-allocated based on the type

of ESI they received: those with unilateral pain received unilateral transforaminal ESI, while those with bilateral pain underwent interlaminar ESI. The patient, research nurse, and evaluating physician were blinded to assignment.

Epidural Injections

All procedures were conducted using fluoroscopic guidance by or under the supervision of a board-certified pain medicine physician. The segmental level at which the injection was administered was selected based on signs, symptoms and radiological findings. For interlaminar injections, a Tuohy needle was inserted in or near the midline and advanced into the epidural space using image guidance in the antero-posterior and lateral views using the loss of resistance technique. For transforaminal ESI, a 22-gauge spinal needle was inserted co-axially into the upper part of the targeted foramina with the imagine intensifier positioned in an oblique plane. Correct placement was confirmed with the injection of contrast, which revealed bilateral spread for all interlaminar injections and proximal epidural uptake for all transforaminal procedures. After the physician was satisfied with the pattern of contrast spread, a solution consisting of 60 mg of depomethylprednisolone + 1 mL of 0.25% bupivacaine was administered. For those who received interlaminar injections, the injectate was diluted in normal saline to a volume of 4 mL; in the transforaminal subgroup, the total volume administered was 3 mL.

Sham Injections & Maintenance of Blinding

Subjects were instructed ahead of time that they may or may not experience paresthesias during the procedure and were visually shielded from the image screen. For all injections, the same technique (e.g. trajectory and use of multiplanar fluoroscopy) was used for sham injections except that the needle was positioned 1-2 cm proximal to the epidural space into the posterior

ligaments. A small volume of saline was then injected in lieu of contrast, followed by 3 additional mL to simulate the injectate. A generic note was entered into the medical record without radiographs.

Pharmacotherapy

300 mg gabapentin and placebo capsules were over-capsulated by a central research pharmacy to appear identical. Prior to each shipment, the capsules were tested to ensure potency, or lack thereof for group 2. Titration schedules were prepared on a case-to-case basis in accordance with standard practice, but dosing targets generally ranged from 1800 mg/d to 3600 mg/d in TID regimens. Medications were generally up-titrated over a period of 15 to 24 days, with the only caveat being that a therapeutic dose range had to be obtained at least 5 days before follow-up.

Co-Interventions, Outcome Measures, Follow-up & Missing Data

No contact with the investigative team was permitted during the study. Tramadol and non-steroidal anti-inflammatory drugs could be prescribed on an "as needed" basis as rescue medications (or opioids could be increased by < 20% for those on opioids), but no other co-interventions were permitted. Subjects were provided with instructions on how to taper their analgesic medications based on response. The first follow-up visit was performed 1-month after treatment initiation by an investigator blinded to treatment. The primary outcome measure was the average 0-10 numerical rating scale (NRS) leg pain score at 1-month, reflecting the average pain experienced during the week before follow-up. Secondary outcome measures included worst leg pain over the past week, average and worst back pain, Oswestry disability index (ODI) score (version 2.0, MODEMS, Des Plaine, IL),[27] adverse effects and complications, reduction in

analgesic medications (> 20% reduction in opioid use or complete cessation of non-opioid analgesics), and global perceived effect (GPE), which was defined as not requiring further non-rescue interventions along with an affirmative response to the following two questions:[28]

1. My pain has improved/ worsened/ stayed the same since my last visit;
2. I am satisfied/ not satisfied with the treatment I received and would/would not recommend it to others.

The Oswestry disability index is a 10-question survey used to assess function in people with low back and/ or leg pain, in which higher scores indicate greater levels of disability. The classification of spinal stenosis was made if the participant had moderate or severe canal stenosis not attributable to a herniated disc. Complications were assessed by fixed and open-ended questions asked 1-day after injections, and at all follow-up visits. In addition to individual variables, a positive composite outcome (i.e. successful procedure) was pre-designated to be a $\geq$ 50% decrease in average leg pain coupled with a positive GPE.

In those individuals who experienced a positive 1-month outcome, the final follow-up occurred at 3 months. For individuals with a positive outcome at 1-month, in addition to rescue medications, the study medication could also be titrated upwards. For ethical reasons, those with a negative 1-month outcome exited the study 'per protocol' to receive non-study interventions, which is consistent with other randomized interventional studies.[26,28-30] In these subjects, 3-month data points for pain scores, ODI and the composite outcome were imputed using the "last-observation-carried-forward" method, which may underestimate effect sizes when "dropouts" are due to lack of efficacy.[31]

Statistical Analysis

An intention-to-treat strategy was used for all analyses. Differences in treatment effects and 95% confidence intervals for pain and disability scores were calculated using analysis of covariance (ANCOVA) with adjustments for baseline values of outcome measures. An indicator of the treatment group was coded such that positive values favored the ESI group. No correction was pre-specified for multiple comparisons. Due to a difference in baseline gender distribution, post hoc analysis of outcomes was adjusted for gender. Logistic-regression models were used to compare the proportion of patients with adverse events in the first month and factors associated with binary outcomes in post-hoc analysis. Analysis of adverse event rates was conducted using Poisson regression models with robust standard errors. Effectiveness of blinding in each treatment group was evaluated using two indices. In the James blinding index[32] (range 0 to 1), 0 indicates total absence of blinding, 1 indicates complete blinding, and 0.5 indicates completely random blinding. In the Bang blinding index[33] (range -1 to 1), -1 indicates all patients guessed the incorrect treatment, 0 indicates all patients randomly guessed, and 1 indicates all patients guessed the correct treatment. Reported P values were based on two-sided tests, with < 0.05 considered statistically significant.

The study was powered to evaluate the effectiveness of ESI compared to gabapentin. Assumptions include a 1.0-point difference in pain scores between groups at 1 month, standard deviation of each group of 2.0, a retention rate of 87%, and a two-sided alpha level of 0.05. If a treatment effect exists between groups, a comparison between 142 randomly assigned individuals would have 80% power to detect a difference of $\geq$ 1.0 point in average leg pain scores at 1 month. Using the data in a post hoc power analysis, the study design had 80% power to detect a 1.22 point difference between groups in 1-month leg pain scores.

Results

348 potential participants were assessed, of whom 147 were eligible for inclusion and agreed to participate. 145 were assigned to receive either an ESI and sham-medication (n=73) or gabapentin and a sham injection (n=72). The two groups were similar with respect to baseline characteristics, except the ESI group had more females (Table 1, Figure 1).

Outcomes

At 1 month, both the ESI group and the gabapentin group experienced improvement in the average leg pain score (-2.2 points [SD 2.4] and -1.7 points [SD 2.6], respectively), but no significant between-group difference was observed (adjusted difference, 0.5 points; 95% confidence interval [CI], -0.2 to 1.3; P=0.174) (Table 2). Small between-group differences favoring ESI were present at 1 month for worst leg pain score (adjusted difference, 1.0 points; 95% CI, 0.1 to 2.0; P=0.026) and successful outcome (67.6% and 47.2%, P=0.014). For average and worst back pain at 1 month, moderate improvements were noted for the ESI (-1.5, SD 1.9) and gabapentin (-1.1, SD 2.3) groups, but the differences were not significant (adjusted difference, 0.3 points; 95% CI, -0.4 to 1.0; P=0.364). At 3 months, no significant differences were observed except for global perceived effect, which favored ESI (51.6% vs. 33.8%; p=0.037).

Factors Associated with Outcome and Post Hoc Analyses

At 1 month, opioid use was associated with a small improvement in leg pain scores for average (-1.0; 95% CI, -0.1 to -1.9; P=0.037) and worst pain (-1.2; 95% CI -0.1 to -2.3; P=0.037) as well as 1 and 3 month composite outcome (P=0.035 and P=0.044, respectively), but no relationship was significant with examination of morphine equivalent doses. Active duty status

was associated with medication reduction at 1 month (P=0.014), global perceived effect at 1 month (P=0.001), and composite outcome at 1 and 3 months (P=0.008 and P=0.010, respectively). Pain duration ≥ 3 months was associated with global perceived effect at 3 months (P=0.009). Otherwise, no associations were found among measures for pain, disability, medication reduction, global perceived effect, or composite outcome at either 1 or 3 months based on opioid use, military status, etiology, pain duration >= 3 months, or injection type. No changes in significance were found between the ESI group and gabapentin group for all outcomes when adjusting for gender.

Adverse Events

The proportion of patients reporting one or more adverse events from the injection was 8.2% in the ESI group and 9.7% in the gabapentin group (P=0.751). The proportion of patients reporting one or more adverse events from the medication was 41.7% in the ESI group and 51.4% in the gabapentin group (P=0.242; table 3).

Blinding

Blinding was assessed at 2 time points, immediately after the procedure to assess blinding for real ESI, and at the first follow-up to ensure blinding for real gabapentin. Immediately following the baseline procedure, patients were unaware of assigned treatments (James blinding index, 0.75; 95% CI, 0.69 to 0.80; P=1; Bing blinding index in ESI group, 0.07; 95% CI, -0.07 to 0.21; Bing blinding index in Gabapentin group, -0.24; 95% CI, -0.38 to -0.09), indicating successful blinding. At 1 month, the overall success of blinding was maintained (James blinding index, 0.56; 95% CI, 0.49 to 0.63; P=0.93), though there was a trend towards better insight into

treatment assignment for the gabapentin group (Bing blinding index in ESI group, 0.08; 95% CI, -0.07 to 0.25; Bing blinding index in Gabapentin group, 0.19; 95% CI, 0.03 to 0.36).

Discussion

The main finding in this double-blind efficacy study is that although some small differences were noted in favor of ESI at 1-month, no statistically significant differences were noted for the primary outcome measure, and the differences observed mostly disappeared at 3-months. Although only a small percentage of our patients had spinal stenosis, our findings are consistent with a recent multi-center study that demonstrated modest, short-term benefit for ESI for this condition.[34] In this study, ESI were compared to epidural local anesthetic, which a systematic review showed was superior to soft-tissue control injections (i.e. not a placebo).[35] In our study, we elected to use a "true placebo" (intramuscular injection), which is more difficult to blind, but unlikely to provide benefit, and included patients with both spinal stenosis and herniated disc. Broad inclusion criteria enhance generalization and are consistent with guidelines on comparative-effectiveness research.[36]

Comparison to Other Studies and Explanation of Findings

Results of placebo-controlled studies evaluating gabapentinoids and other membrane stabilizers for radiculopathy are mixed, indicating a probable small effect size.[37] This suggests that differences between groups are unlikely to represent a large treatment effect. Although myriad reviews on ESI have yielded disparate conclusions, recent systematic and evidence-based reviews have indicated that any stand-alone treatment effect for ESI is likely to be modest and short-lived.[12,22]

There are several possible explanations for our findings. The first is that both treatments are equally effective, but the effects dissipate over time. Unlike studies for ESI which frequently follow patients for up to one year,[38-43] few studies have examined the long-term effectiveness of gabapentin, but those that have indicate that the beneficial effects for neuropathic pain are most

pronounced early on during treatment.[44,45] A second hypothesis is that neither treatment is effective, and the benefits observed were due to a placebo response or the natural course of the disease. However those with chronic radiculopathy are less likely to spontaneously improve or respond to treatment than those with shorter duration of symptoms.[46] A third possibility is that ESI are superior to gabapentin, but the relatively small sample size, allowing only one ESI, treatment blinding, and our failure to reinforce the short-term benefit with physical therapy rendered 3-month differences indistinguishable. In a comparative-effectiveness study that compared a series of ESI to neuropathic adjuvants plus physical therapy to combination therapy for cervical radiculopathy, the combination group fared better than both stand-alone treatments.[26]

Limitations

There are several limitations to our study, including the relatively small size and the lack of a placebo group. A third limitation is that we did not permit repeat ESI or allow combination drug treatment. Studies have demonstrated there is little basis for a rote "series" of ESI, though some may benefit from repeat injections, which are often performed in clinical practice.[12,26,28,34,43,47,48] Similarly, randomized studies have shown that combination therapy with drugs that include gabapentinoids may provide superior relief for neuropathic and LBP compared to single agent treatment.[49] A fourth limitation inherent in our design is that blinding subjects may have altered our findings. "Blinding" is not a tenet of comparative-effectiveness research, which seeks to determine the best treatment in "real-world" conditions. The placebo effect is especially powerful for subjective measures such as pain, and stronger for procedures than pills, which may have mitigated any "real-world" differences between treatments.[50,51] A final limitation is our broad inclusion criteria which included patients on opioids, and those with herniated disc and spinal stenosis. In practice, patients generally receive ESI and/or adjuvants

regardless of the etiology of their neuropathic pain. In clinical trials, most ESI [12,24-26,28,38,40,42] and all gabapentinoid studies [17-21] included both etiologies, with a majority of studies finding no difference in ESI[12] or gabapentinoid (personal communication from Ralf Baron 10-9-2014)[20,21] outcomes between stenosis and disc herniation.

Generalizability

These results are readily generalizable to primary care settings, pain physicians, and surgeons, where practitioners are often faced with the question about the best non-operative way to manage sciatica. Future studies might include both placebo and combination groups, allow for multiple injections and medications, and require physical therapy in an effort to determine whether any benefit that is observed could be prolonged. However, the logistical and ethical obstacles in designing such studies (e.g. blinding multiple medications or performing multiple sham injections in patients who fail to respond to the first one) will make them difficult to execute. Until these studies are performed, the decision as to which treatment path to initiate for sciatica should be based on clinical concerns (i.e. need to stop anticoagulants, concerns about missing work, sensitivity to medication effects) and patient preference.

Conclusions

Gabapentin and ESI both resulted in modest improvements in pain and function which persisted through 3 months. Although some differences favored ESI at 1-month, these tended to be small and transient. The decision as to which non-surgical treatment to utilize should therefore depend on patient-related factors.

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Table 1. Baseline demographic and clinical characteristics of study subjects[1]

Characteristic	Epidural Steroid Injection Group (n = 73)	Gabapentin Group (n = 72)
Age – years	43.8 ± 14.0	41.7 ± 11.9
Female sex – no. (%)[2]	25 (34.2)	13 (18.1)
Duration of pain - no. (%)		
< 3 months	11 (15.1)	15 (20.8)
3 to < 12 months	26 (25.6)	27 (37.5)
1 to 3 years	27 (37.0)	23 (31.9)
> 3 years	9 (12.3)	7 (9.7)
Opioid therapy – no. (%)		
No opioids	54 (74.0)	55 (76.4)
< 60 morphine equivalents/day	16 (21.9)	14 (19.4)
>= 60 morphine equivalents/day	3 (4.1)	3 (4.2)
Average morphine equivalents among opioid users	28.7 (34.8)	38.5 (53.0)
Diagnosis – no. (%)		
Herniated nucleus pulposus	63 (84.9)	65 (90.3)
Spinal stenosis	10 (13.7)	7 (9.7)
Active duty military - no. (%)	38 (52.0)	41 (56.9)
Enlisted	26 (35.6)	30 (41.7)
Officer	12 (16.4)	11 (15.3)
Inciting event – no. (%)		
None	42 (57.5)	41 (56.9)
Motor Vehicle Accident	1 (1.4)	1 (1.4)
Fall	5 (6.9)	9 (12.5)
Lifting	13 (17.8)	6 (8.3)
Sports/Training	8 (11.0)	13 (18.1)
Other[3]	4 (5.5)	2 (2.8)
Pain related to deployment – no. (%)	10 (13.7)	6 (8.3)
Current smoker – no. (%)[4]	15 (20.6)	13 (18.1)
Obesity – no. (%)	13 (17.8)	19 (26.4)
Psychiatric comorbidity – no. (%)		
None	56 (76.7)	49 (68.1)
Mood	9 (12.3)	12 (16.7)
Anxiety	7 (9.6)	6 (8.3)
Substance abuse	3 (4.1)	4 (5.6)
Posttraumatic stress disorder	1 (1.4)	4 (5.6)
Other[5]	1 (1.4)	3 (4.2)
Multiple diagnoses	4 (5.5)	6 (8.3)
Injection approach – no. (%)		
Interlaminar	11 (15.1)	12 (16.7)
Transforaminal	62 (84.9)	60 (83.3)
Level of injection – no. (%)		
L2-3	1 (1.4)	0 (0)

L3-4	1 (1.4)	2 (2.8)
L4-5	22 (30.1)	18 (25.0)
L5-S1	44 (60.3)	46 (63.9)
S1	5 (6.9)	6 (8.3)
Baseline pain scores[6]		
Average Leg Pain	5.4 ± 2.1	5.4 ± 1.9
Worst Leg Pain	7.9 ± 1.7	7.8 ± 2.0
Average Back Pain	5.0 ± 2.6	4.7 ± 2.4
Worst Back Pain	7.0 ± 2.6	7.0 ± 2.9
Baseline Oswestry Disability Score	39.8 ± 15.3	39.8 ± 14.7

1. Plus–minus values are means ± SD.
2. The difference between the two groups was significant (P = 0.027 by the chi-squared test).
3. Other inciting events include post-surgical, pregnancy, spinal tap and work-related.
4. Smoking includes 3 participants who chew tobacco products.
5. Other psychiatric comorbidities include attention deficit hyperactivity disorder and obsessive-compulsive disorder.
6. Based on 0-10 numerical rating scale scores

Table 2. Outcomes according to treatment group.[1]

	Epidural Steroid Injection Group			Gabapentin Group			Treatment Comparison	
	No. of Patients	Overall Mean	Mean Change from Baseline	No. of Patients	Overall Mean	Mean Change from Baseline	Adjusted Difference (95% CI)[2]	P Value
Average Leg Pain								
Baseline	73	5.4 ± 2.1	-	72	5.4 ± 1.9	-	-	-
4 weeks	71	3.2 ± 2.5	-2.2 ± 2.4	72	3.7 ± 2.6	-1.7 ± 2.6	0.5 (-0.2 to 1.3)	0.174
12 weeks	64	3.4 ± 2.7	-2.0 ± 2.7	71	3.8 ± 2.8	-1.5 ± 2.7	0.5 (-0.4 to 1.4)	0.271
Worst Leg Pain								
Baseline	73	7.9 ± 1.7	-	72	7.8 ± 2.0	-	-	-
4 weeks	71	4.8 ± 3.0	-3.0 ± 2.8	72	5.8 ± 3.0	-2.0 ± 2.9	1.0 (0.1 to 2.0)	0.026
12 weeks	64	5.0 ± 3.4	-2.7 ± 3.3	71	5.6 ± 3.4	-2.2 ±3.4	0.5 (-0.6 to 1.7)	0.341
Average Back Pain								
Baseline	73	5.0 ± 2.6	-	72	4.7 ± 2.4	-	-	-
4 weeks	71	3.5 ± 2.6	-1.5 ± 1.9	72	3.6 ± 2.6	-1.1 ± 2.3	0.3 (-0.4 to 1.0)	0.364
12 weeks	64	4.0 ± 2.7	-1.1 ± 2.5	71	3.8 ± 2.5	-0.9 ± 2.3	0.0 (-0.7 to 0.8)	0.970
Worst Back Pain								
Baseline	73	7.0 ± 2.6	-	72	7.0 ± 2.9	-	-	-
4 weeks	71	5.0 ± 2.8	-2.0 ± 2.4	72	5.4 ± 3.2	-1.6 ± 2.6	0.4 (-0.4 to 1.2)	0.301
12 weeks	64	5.6 ± 3.2	-1.4 ± 2.9	71	5.8 ± 3.1	-1.2 ± 2.5	0.2 (-0.7 to 1.1)	0.624
Oswestry Disability Score[3]								
Baseline	73	39.8 ± 15.3	-	72	39.8 ± 14.7	-	-	-
4 weeks	71	32.0 ± 18.2	-7.5 ± 12.7	72	29.6 ± 16.0	-10.2 ± 14.5	-2.7 (-7.0 to 1.7)	0.226
12 weeks	64	33.5 ± 19.7	-6.0 ± 16.6	71	29.9 ± 16.3	-10.1 ± 16.8	-3.9 (-9.3 to 1.4)	0.141
Medication Reduction – no. (%)[4]								
4 weeks	67	40 (59.7)	-	65	32 (49.2)	-	-	0.227

12 weeks	40	23 (57.5)	-	30	14 (46.7)	-	-	0.369
Global Perceived Effect (positive) – no. (%)								
4 weeks	71	49 (69.0)	-	72	41 (56.9)	-	-	0.135
12 weeks	64	33 (51.6)	-	71	24 (33.8)	-	-	0.037
Composite Outcome (positive) - no. (%)[5]								
4 weeks	71	48 (67.6)	-	72	34 (47.2)	-	-	0.014
12 weeks	64	27 (42.2)	-	71	21 (29.6)	-	-	0.126

1. Plus-minus values are means ± SD. CI denotes confidence interval. Imputed data from 1 month was carried over to 3 months for treatment failures for pain scores, Oswestry disability scores, global perceived effect and composite outcome. Numerical rating scores for pain are based on 0-10 numerical rating scales, with 0 indicating no pain and 10 indicating severe pain.
2. Differences for pain and Oswestry disability scores were adjusted for baseline outcome values. Negative coefficients favor the gabapentin group. Positive coefficients favor the epidural steroid injection group.
3. The Oswestry disability index is a 10-question survey used to assess function in people with low back and/ or leg pain, in which higher scores indicate greater levels of disability. [26]
4. Reduction in analgesic medications corresponds to > 20% reduction in opioid use or complete cessation of non-opioid analgesic.
5. Defined as ≥ 2-point decrease in average leg pain coupled with a positive global perceived effect without additional procedural or non-rescue pharmacological interventions.

Table 3. Adverse Events [1]

Adverse Event	Epidural Steroid Injection Group (n = 73)	Gabapentin Group (n = 72)	P-Value
Injection	**Epidural Steroid Injections**	**Sham Injection**	
≥1 event – no. of patients (%)[2]	6 (8.2)	7 (9.7)	0.751
Total adverse events – no. of events (event rate)[3]	6 (0.08)	9 (0.13)	0.422
Reported symptoms or events – no. (%)			
Excessive pain	2[7]	4[7]	
Fever, infection, or both	2	0	
Falls	1[7]	0	
Vasovagal	0	2[7]	
Other[4]	1	3	
Medication	**Sham Pills**	**Gabapentin Pills**	
Dose (mg)	2132.9 ± 609.4	2095.8 ± 678.3	0.730
Compliance - no. (%)[5]			
None	6 (8.3)	8 (11.1)	0.681
Partial (50-89%)	11 (15.3)	8 (11.1)	
Full (>90%)	55 (76.4)	56 (77.8)	
≥1 event – no. of patients (%)[2,5]	30 (41.7)	37 (51.4)	0.242
Total adverse events – no. of events (event rate)[3,5]	45 (0.63)	50 (0.69)	0.609
Reported symptoms or events – no. (%)[5]			
Sedation/ Fatigue	8 (11.1)	13 (18.1)[7]	
Cognitive	5 (6.9)	7 (9.7)[7]	
Weight gain	4 (5.6)	7 (9.7)[7]	
Headache	4 (5.6)	1 (1.4)	
Gastrointestinal	13 (18.1)	8 (11.1)[7]	
Swelling	0 (0)	3 (4.2)[7]	
Other[6]	11 (15.3)	11 (15.3)[7]	

1. Plus–minus values are means ± SD.
2. Statistical significance was assessed using logistic regression model adjusted for treatment group assignment.
3. Statistical significance was assessed using a Poisson regression model with robust standard errors adjusted for treatment group assignment.

4. Other adverse events for epidural steroid injection group include 'low cortisol noted on labs 3 weeks after injection in a patient also on oral steroids with no symptoms'. Other adverse events for gabapentin group (sham injection) include bruising, temporary inability to lift legs, and 'GI bleed after 3 days in a patient on low molecular weight heparin'. None were deemed related to treatment.
5. Data were missing for one patient in the epidural steroid injection group.
6. For medication, other adverse events for epidural steroid injection group (placebo pills) include ataxia, balance problems, depression, emotionality, kidney stones, muscle twitching, hot flashes, restlessness, rhinorrhea with congestion, sexual, vivid dreams, and one without description. Other adverse events for gabapentin group include blackout,[7] depression requiring hospitalization, dizziness (2),[7] dry mouth (2),[7] leg spasms, mood changes, rhinorrhea with flu-like symptoms, and one with no description.
7. Deemed related or possibly related to treatment.

Figure Legend

Figure 1. CONSORT study flow diagram

What is already known about this topic: Both gabapentin and epidural steroid injections are frequently used to treat lumbosacral radiculopathy and may provide benefit for a subset of patients, but we do not know which treatment works better.

What this study adds: Although epidural steroid injections may be superior to gabapentin in some outcome measures, the differences are small and short-lived.

Author Contributions:

SPC: Designed study, wrote protocol, served as overall PI, performed treatments, wrote and reviewed manuscript

SH, YV, RLW, KBG, ZZ: Site PI, performed treatments, reviewed manuscript

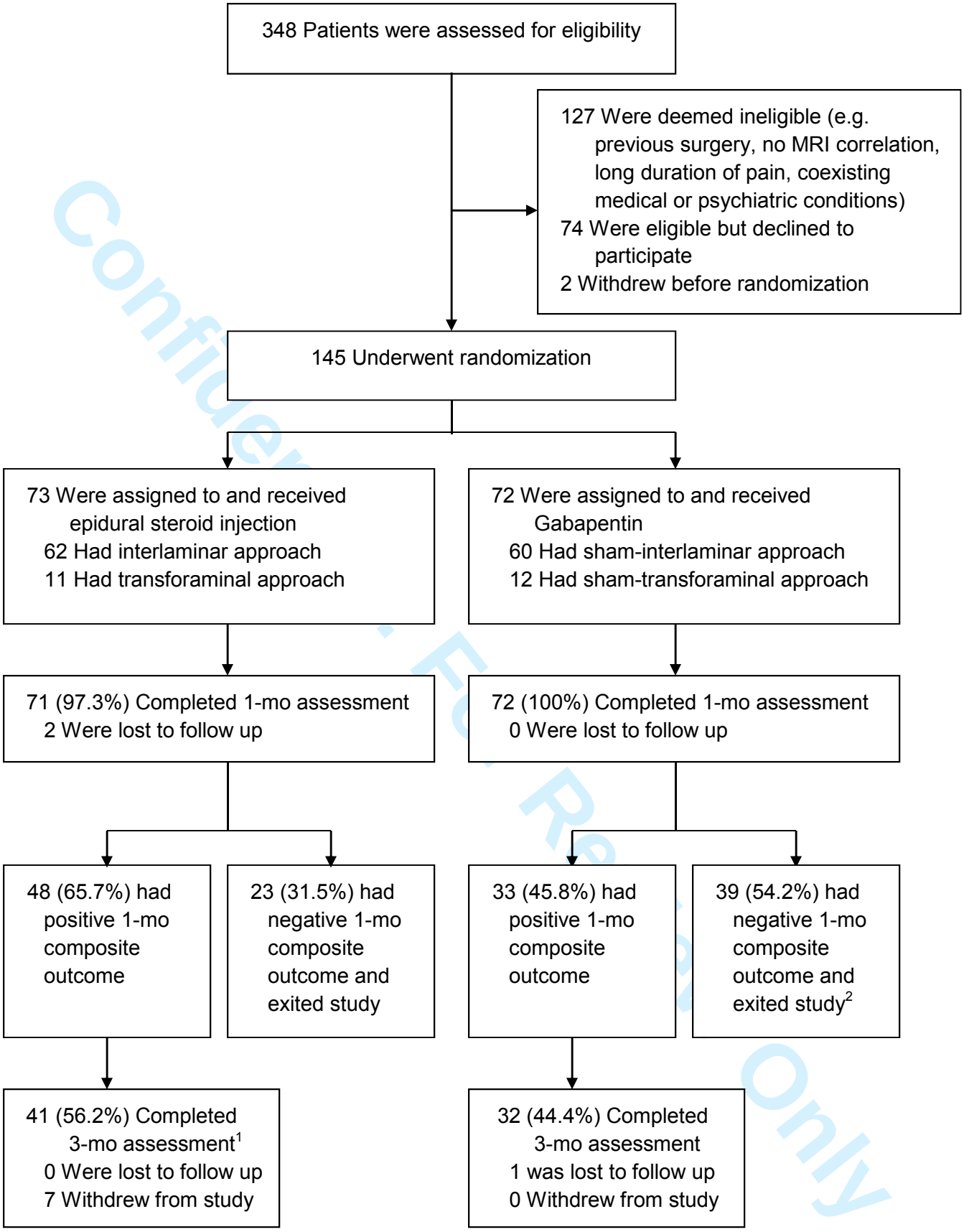
SRG, VG, EV: Assisted with protocol adaptation for individual sites, performed treatments, reviewed manuscript

MAW, CK: Research nurses (CK was Chief research nurse), collected data, assisted with protocol adaptations and submissions

MCB: Helped write manuscript, statistical analysis

PFP: Helped design study, funding source, critical review of manuscript

SPC and PFP are guarantors



1. This total includes 8 participants with early 3-month evaluations because of return of pain to baseline.
2. This includes 1 participant who sought emergency care and 1 patient with unstable angina who was started on opioids, both unrelated to treatment.