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Original Investigation

Oral Steroids for Acute Radiculopathy Due to a Herniated Lumbar Disk

A Randomized Clinical Trial

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IMPORTANCE Oral steroids are commonly used to treat acute sciatica due to a herniated disk but have not been evaluated in an appropriately powered clinical trial.

OBJECTIVE To determine if oral prednisone is more effective than placebo in improving function and pain among patients with acute sciatica.

DESIGN, SETTING, AND PARTICIPANTS Randomized, double-blind, placebo-controlled clinical trial conducted from 2008 to 2013 in a large integrated health care delivery system in Northern California. Adults (n=269) with radicular pain for 3 months or less, an Oswestry Disability Index (ODI) score of 30 or higher (range, 0-100; higher scores indicate greater dysfunction), and a herniated disk confirmed by magnetic resonance imaging were eligible.

INTERVENTIONS Participants were randomly assigned in a 2:1 ratio to receive a tapering 15-day course of oral prednisone (5 days each of 60 mg, 40 mg, and 20 mg; total cumulative dose = 600 mg; n = 181) or matching placebo (n = 88).

MAIN OUTCOMES AND MEASURES The primary outcome was ODI change at 3 weeks; secondary outcomes were ODI change at 1 year, change in lower extremity pain (measured on a 0-10 scale; higher scores indicate more pain), spine surgery, and Short Form 36 Health Survey (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) scores (0-100 scale; higher scores better).

RESULTS Observed baseline and 3-week mean ODI scores were 51.2 and 32.2 for the prednisone group and 51.1 and 37.5 for the placebo group, respectively. The prednisone-treated group showed an adjusted mean 6.4-point (95% CI, 1.9-10.9; $P = .006$) greater improvement in ODI scores at 3 weeks than the placebo group and a mean 7.4-point (95% CI, 2.2-12.5; $P = .005$) greater improvement at 52 weeks. Compared with the placebo group, the prednisone group showed an adjusted mean 0.3-point (95% CI, -0.4 to 1.0; $P = .34$) greater reduction in pain at 3 weeks and a mean 0.6-point (95% CI, -0.2 to 1.3; $P = .15$) greater reduction at 52 weeks. The prednisone group showed an adjusted mean 3.3-point (95% CI, 1.3-5.2; $P = .001$) greater improvement in the SF-36 PCS score at 3 weeks, no difference in the SF-36 PCS score at 52 weeks (mean, 2.5; 95% CI, -0.3 to 5.4; $P = .08$), no change in the SF-36 MCS score at 3 weeks (mean, 2.2; 95% CI, -0.4 to 4.8; $P = .10$), and an adjusted 3.6-point (95% CI, 0.6-6.7; $P = .02$) greater improvement in the SF-36 MCS score at 52 weeks. There were no differences in surgery rates at 52-week follow-up. Having 1 or more adverse events at 3-week follow-up was more common in the prednisone group than in the placebo group (49.2% vs 23.9%; $P < .001$).

CONCLUSIONS AND RELEVANCE Among patients with acute radiculopathy due to a herniated lumbar disk, a short course of oral steroids, compared with placebo, resulted in modestly improved function and no improvement in pain.

TRIAL REGISTRATION clinicaltrials.gov Identifier: NCT00668434

JAMA. 2015;313(19):1915-1923. doi:10.1001/jama.2015.4468

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Acute lumbar radiculopathy (sciatica) is characterized by radiating buttock and leg pain in a lumbar nerve root distribution.^{1,2} It is commonly associated with the herniation of the nucleus pulposus^{3,4} and has a lifetime prevalence exceeding 10%.⁵ Spontaneous recovery occurs in most patients; however, many endure substantial pain and disability.^{2,3,6} For those who do not recover quickly, invasive procedures such as epidural steroid injections (ESIs) and lumbar discectomy are commonly performed.^{3,7,8} Accelerating the process of recovery would provide substantial benefits to affected patients and potentially reduce the need for expensive invasive procedures.

ESI epidural steroid injection

MRI magnetic resonance imaging

NRS numerical rating scale

ODI Oswestry Disability Index

Despite conflicting evidence, ESIs are frequently offered under the assumption that radicular symptoms are caused by inflammation of the affected lumbar nerve root.^{4,9-11} Epidural steroid injections are invasive, generally require a preprocedure magnetic resonance imaging (MRI) study, and expose patients to fluoroscopic radiation. In addition, the US Food and Drug Administration recently warned of rare but serious neurologic sequelae from ESIs.^{12,13} Oral administration of steroid medication may provide similar anti-inflammatory activity, does not require an MRI or radiation exposure, can be delivered quickly by primary care physicians, carries less risk, and would be much less expensive than an ESI. Oral steroids are used by many community physicians, have been included in some clinical guidelines,¹⁴ and are noted as a treatment option by some authors.^{15,16} However, no appropriately powered clinical trials of oral steroids for radiculopathy have been conducted to date.¹⁷

To address this issue, we performed a parallel-group, double-blind randomized clinical trial of a 15-day tapering course of oral prednisone vs placebo for patients with an acute lumbar radiculopathy associated with a herniated lumbar disk. The trial protocol is available in the Supplement.

Methods

Participants

Eligible patients (Figure 1) were members of Kaiser Permanente Northern California, were aged 18 to 70 years, reported leg pain extending below the knee in a nerve root distribution, had a herniated disk confirmed by MRI, and scored 30 points or higher on the Oswestry Disability Index¹⁸ (ODI; this cut point was chosen from a pilot study as the approximate median ODI score among similar patients). Exclusion criteria included onset of radicular pain more than 3 months prior, previous lumbar surgery, oral or epidural steroid treatment in the prior 3 months, diabetes, substantial or progressive motor loss, and/or ongoing litigation or workers compensation claim. A positive straight-leg raise test result was initially an inclusion criterion that was eliminated after 14 months to improve recruitment and allow interaction analyses with this characteristic. Participants were recruited from primary care practices at 3 Kaiser Permanente Northern

California facilities and from a daily extract of the electronic medical record. Race/ethnicity data were self-reported. (This National Institutes of Health–funded study was required to collect and annually report data on race and ethnicity for all participants. We used these data in preplanned subgroup analyses examining potential interaction with demographic variables; see section 2.3 of the trial protocol in the Supplement.)

Intervention

Participants randomized to the active treatment group took three 20-mg capsules of prednisone daily for 5 days, then 2 capsules daily for 5 days, then 1 capsule daily for 5 days (this cumulative dose of 600 mg was thought to provide sufficient anti-inflammatory effect and was in common use in local practice). Participants in the placebo group received identical-appearing capsules and instructions. Nonsteroidal anti-inflammatory drugs were not allowed for 3 weeks after randomization, but otherwise all patients in both treatment groups received usual care for their symptoms.

Outcomes

The primary outcome was self-reported score on the ODI, version 2.0 (measured on a 0- to 100-point scale, with higher scores indicating greater dysfunction)¹⁸ measured 3 weeks after randomization. We chose this time point for the primary outcome because we were most interested in testing whether oral steroids could more rapidly return patients to higher functioning and less pain in the early, more symptomatic weeks of an acute sciatica episode. Predefined secondary outcomes were a pain numerical rating scale (NRS) scored on a 0- to 10-point scale (higher numbers indicating more pain) that inquired about participants' average, best, and worst levels of pain below the waist over the prior 3 days and participants' average pain levels above the waist, the Short Form 36 Health Survey Physical Component Summary and Mental Component Summary subscale scores (each measured on 0- to 100-point scales, with higher scores indicating better health status),¹⁹ and incidence of lumbar spine surgery. An additional measure assessed participants' global assessment of improvement by asking participants to rate how much their leg pain had changed since taking the study medication (measured on a Likert scale from 1 [very much better] to 7 [very much worse]).

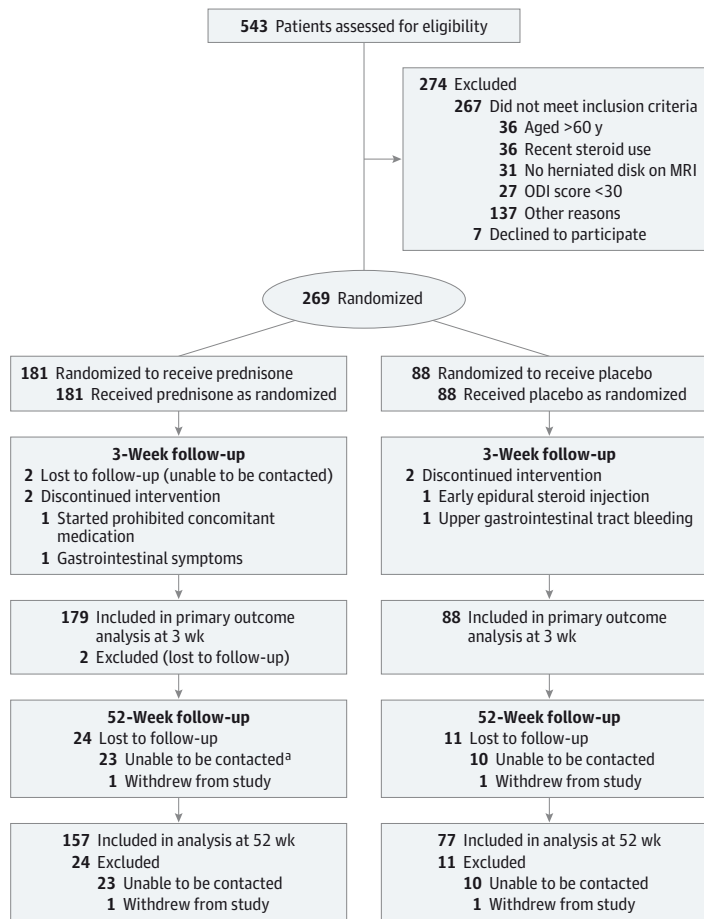
Study Procedures

After providing informed consent, patients were reviewed for eligibility by a spine-specialist physician. The presence of a herniated lumbar disk was established by concordance between 2 independent readings of the patient's lumbar spine MRI by 2 spine physicians or a spine physician and a neuroradiologist.

Randomization was performed using variable block sizes and implemented by the University of California, San Francisco Compounding Pharmacy, which provided pre-filled medication bottles according to a randomization list generated by nonstudy personnel. Study investigators, staff, and participants were blinded to treatment assignment.

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Figure 1. Flow of Participants in Randomized, Double-Blind Trial of Oral Prednisone vs Placebo Through 3-Week (Primary) and 52-Week (Secondary) Follow-up



MRI indicates magnetic resonance imaging; ODI, Oswestry Disability Index.

^a One of the 2 participants lost to follow-up for the entire study after the baseline visit. The other participant was contacted and included in the final 52-week follow-up.

Participants were seen in the clinic at 3 weeks and 24 weeks after randomization and were telephoned at 6, 12, and 52 weeks. By protocol, patients who did not describe themselves as at least “much better” on the patient global assessment item and whose ODI score remained higher than 30 points were offered ESIs at 3 and 6 weeks after randomization but could also be referred for an ESI by their physician at any time.

The occurrence of adverse events was ascertained at each study contact. Study progress was reviewed regularly by a data and safety monitoring board constituted by the National Institute of Arthritis and Musculoskeletal and Skin Diseases. All study procedures were approved by the institutional review board of the Kaiser Foundation Research Institute; written informed consent was obtained from all participants.

The first participant was randomized in November 2008; the last participant assessment occurred in August 2013.

Statistical Analysis

The trial had sufficient statistical power for a 90% probability of detecting a difference of 7.0 points or more on the ODI at 3 weeks, assuming a standard deviation in ODI scores of 15.1, with a randomization ratio of 2:1 and a 2-sided $\alpha = .047$ (to allow for up to 2 interim analyses).²⁰ The intergroup difference

of 7.0 points was within the range of published estimates of the minimum clinically important difference for the ODI.²¹⁻²⁸ These calculations required an evaluable sample of 226 participants; assuming a potential 20% withdrawal rate, the final intended sample size was 270 participants.

Unadjusted analyses were conducted using the *t* test for continuous and ordinal variables and were consistent with the corresponding Wilcoxon rank sum tests. Categorical variables (including the responder analyses) were analyzed with the Fisher exact test or its generalization for more than 2 levels.²⁹ Adjusted analyses for continuous and ordinal variables were conducted with multivariable linear regression models, assessed for model fit and departures from the modeling assumptions. For dichotomous outcome variables, adjusted risk ratios were obtained from multivariable Poisson regression models using robust (Huber-White) standard errors.³⁰ The final models included adjustments for baseline demographics, study site, presence of a positive straight-leg raise test result at baseline, and elapsed time between symptom onset and randomization. Continuous outcomes were dichotomized at several cut points for a set of exploratory, post hoc responder analyses. All analyses were conducted under the principle of intention to treat in that all participants were analyzed in the

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Table 1. Baseline Demographic and Clinical Characteristics Overall and by Study Group

Characteristics	All Participants (N = 269)	Prednisone Group (n = 181)	Placebo Group (n = 88)
Age, mean (SD), y	46.0 (12.1)	45.6 (11.8)	46.7 (12.6)
Male, No. (%)	149 (55.4)	98 (54.1)	51 (58.0)
Race, No. (%) ^a			
Native American	5 (1.9)	1 (0.6)	4 (4.6)
Asian	32 (11.9)	24 (13.3)	8 (9.1)
African American	6 (2.2)	3 (1.7)	3 (3.4)
Pacific Islander	2 (0.7)	2 (1.1)	0
White	179 (66.5)	129 (71.3)	50 (56.8)
>1 Race	19 (7.1)	10 (5.5)	9 (10.2)
Declined to state race	26 (9.7)	12 (6.6)	14 (15.9)
Ethnicity, No. (%) ^b			
Hispanic	62 (23.1)	34 (18.8)	28 (31.8)
Education, No. (%)			
High school graduate or lower	68 (25.3)	46 (25.4)	22 (25.0)
Some college	95 (35.3)	65 (35.9)	30 (34.1)
College graduate or higher	106 (39.4)	70 (38.7)	36 (40.9)
Oswestry Disability Index score, mean (SD) ^c	51.1 (13.5)	51.2 (14.5)	51.1 (11.5)
Below-waist pain numerical rating scale score, mean (SD) ^d	6.7 (1.9)	6.6 (2.0)	6.9 (1.8)
Time from pain onset to randomization, d			
Mean (SD)	30.4 (21.4)	29.7 (20.8)	31.7 (22.7)
Median (interquartile range)	25 (14-42)	25 (14-38)	27 (12-48)
Positive straight-leg raise test result, No. (%)	224 (88.4)	154 (85.1)	70 (79.6)
Muscle weakness at baseline, No. (%) ^e	14 (5.2)	8 (4.4)	6 (6.8)
Short Form 36 Health Survey score, mean (SD)			
Physical Component Summary ^f	30.6 (6.6)	30.4 (6.8)	30.9 (6.2)
Mental Component Summary ^g	48.7 (11.8)	48.5 (11.6)	49.3 (12.3)

^a $P=.009$ for prednisone group vs placebo group.

^b $P=.02$ for prednisone group vs placebo group.

^c Score range, 0-100; higher scores indicate greater dysfunction.

^d Score range, 0-10; higher scores indicate more pain.

^e Defined as score ≤ 3 on 0- to 5-point scale for lower extremity motor strength scoring.

^f Score range, 0-100; higher scores indicate better physical health status.

^g Score range, 0-100; higher scores indicate better mental health status.

group to which they were randomized, regardless of adherence. For the 52-week data, all models were fit to 50 multiple-imputed data sets using a Markov chain Monte Carlo method.³¹ All reported P values are 2-sided, with $P < .05$ signifying statistical significance, and no adjustments were made for multiple hypothesis testing. All analyses were conducted with Stata software, version 13.1.³¹

Seven subgroup analyses were prespecified (numbers in each group shown in brackets): median baseline severity of symptoms (ODI score ≤ 48 vs >48 [$n=140$ vs $n=129$]), presence of baseline ipsilateral motor weakness (muscle strength score 0-3 vs 4-5 on a 0- to 5-point scale, with higher scores indicating greater strength [$n=14$ vs $n=255$]), median time between onset of symptoms and randomization (≤ 25 days vs >25 days [$n=137$ vs $n=132$]), median age (≤ 46 vs >46 years [$n=137$ vs $n=132$]), sex (male vs female [$n=149$ vs $n=120$]), race (white vs nonwhite [$n=179$ vs $n=90$]), and ethnicity (Hispanic vs non-Hispanic [$n=62$ vs $n=207$]). Other subgroups examined were median baseline pain score (≤ 6 vs >6 [$n=107$ vs $n=162$]) and straight-leg raise test (positive vs negative result [$n=224$ vs $n=45$]). All subgroup analyses were performed using interaction terms in the multivariable regression models.

Results

Of the 543 individuals screened, 269 met eligibility criteria and were enrolled (Figure 1). The most common reasons for ineligibility were related to age, radiographic findings, severity or duration of symptoms, or current steroid treatment.

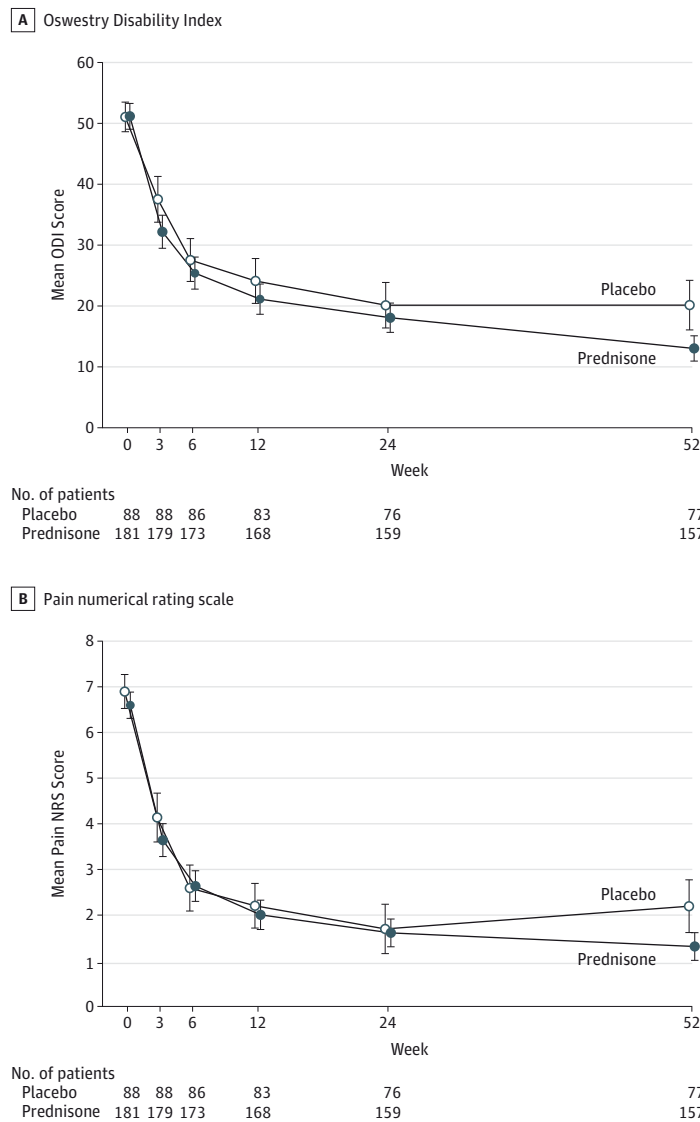
Treatment groups were generally well matched at baseline (Table 1), although participants randomized to prednisone included a higher prevalence of white patients and a lower prevalence of reporting more than 1 race, declining to state a race, and Hispanic ethnicity.

The primary outcome visit at 3 weeks was attended by 267 participants (99.3%), and the secondary 52-week outcome assessment was completed by 234 participants (87.0%). Two hundred fifty-four (95.5%) of 266 participants for whom adherence data were available took all their study medication and 263 (98.9%) took at least 75% of their study medication.

Participants in both blinded treatment groups showed an improvement in symptoms over the initial 6 weeks, with more gradual reductions until the 24-week visit, after which changes were more variable (Figure 2). Baseline ODI scores were 51.2

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Figure 2. Scores on the Oswestry Disability Index and Pain Numerical Rating Scale



Observed mean values for the (A) Oswestry Disability Index (ODI) and (B) pain numerical rating scale (NRS) for average pain below the waist in the prior 3 days in the prednisone-treated and placebo-treated groups. The ODI is measured on a 0- to 100-point scale, with higher numbers indicating more functional disability. The pain NRS is measured on a 0- to 10-point scale, with higher numbers indicating more pain. Treatment occurred during the first 15 days after randomization. Errors bars indicate 95% CIs.

and 51.1 in the prednisone and placebo groups, respectively; corresponding ODI scores at 3 weeks were 32.2 and 37.5. At 3 weeks, participants in the prednisone-treated group showed an unadjusted mean 5.6-point (95% CI, 1.1-10.1; $P = .01$) greater reduction in ODI scores compared with participants in the placebo group (Figure 2A). At 52 weeks, the mean between-group difference was 7.6 points (95% CI, 2.6-12.7; $P = .003$). After statistical adjustment, the between-group differences also favored prednisone at 3 weeks (mean difference, 6.4 points; 95% CI, 1.9-10.9; $P = .006$) and at 52 weeks (mean difference, 7.4 points; 95% CI, 2.2-12.5; $P = .005$) (Table 2).

In a responder analysis, the prednisone-treated group showed a significantly greater relative likelihood of achieving at least a 30-point or 50% improvement in the ODI at 3 weeks (relative risk [RR], 1.7; 95% CI, 1.1-2.9; number needed to treat [NNT], 10.6 and RR, 1.8; 95% CI, 1.1-2.9; NNT, 7.6, respectively) and at 52 weeks (RR, 1.3; 95% CI, 1.0-1.6; NNT, 7.1 and RR, 1.2; 95% CI, 1.1-1.5; NNT, 5.5, respectively) (Table 2).

Unlike the ODI, there was no statistically significant difference between groups in changes in the below-waist pain NRS at either the 3-week or 52-week time points (Table 2 and Figure 2B). Similarly, there were no significant differences between groups in the proportion of participants achieving at least a 2-, 3-, or 5-point improvement in the pain NRS scores at either time point (Table 2).

Participants randomized to prednisone had a significantly greater improvement in the Physical Component Summary score of the Short Form 36 at 3 weeks (by a mean of 3.3 points; 95% CI, 1.3-5.2; $P = .001$) and the Mental Component Summary score at 1 year (by a mean of 3.6 points; 95% CI, 0.6-6.7; $P = .02$) (Table 2).

Over the 1-year follow-up period, there was no significant between-group difference in the likelihood of undergoing spine surgery (9.9% vs 9.1%; RR, 1.2; 95% CI, 0.5-2.6; $P = .68$) (Table 2).

The global patient assessment outcome, an exploratory outcome, was measured with a dynamic perceived change in

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Table 2. Changes in Outcome Measures From Baseline to 3-Week and 52-Week Follow-up

Outcomes	3-Week Follow-up			52-Week Follow-up			
	Prednisone Group (n = 179)	Placebo Group (n = 88)	Adjusted Difference Between Groups (95% CI) ^a	Prednisone Group (n = 157)	Placebo Group (n = 77)	Adjusted Difference Between Groups (95% CI) ^a	P Value
Primary outcome, mean (95% CI)							
Oswestry Disability Index score ^b	-19.0 (-21.6 to -16.3)	-13.3 (-16.7 to -10.0)	-6.4 (-10.9 to -1.9)	-37.8 (-40.7 to -35.0)	-30.4 (-34.8 to -25.9)	-7.4 (-12.5 to -2.2)	.005
Other continuous outcomes, mean (95% CI)							
Pain numerical rating scale score ^c							
Below waist, average	-3.0 (-3.3 to -2.6)	-2.8 (-3.3 to -2.2)	-0.3 (-1.0 to 0.4)	-5.2 (-5.6 to -4.7)	-4.6 (-5.2 to -4.0)	-0.6 (-1.3 to 0.2)	.15
Below waist, worst	-3.6 (-4.0 to -3.1)	-3.2 (-3.8 to -2.6)	-0.5 (-1.3 to 0.3)	-6.5 (-7.0 to -6.1)	-5.7 (-6.4 to -5.0)	-0.7 (-1.6 to 0.1)	.09
Below waist, least	-2.0 (-2.4 to -1.6)	-1.5 (-2.1 to -1.0)	-0.5 (-1.2 to 0.2)	-3.4 (-3.8 to -2.9)	-3.0 (-3.6 to -2.3)	-0.4 (-1.1 to 0.4)	.33
Above waist, average	-1.0 (-1.3 to -0.6)	-0.8 (-1.3 to -0.3)	-0.2 (-0.8 to 0.5)	-1.5 (-2.0 to -1.0)	-1.4 (-2.0 to -0.7)	-0.2 (-1.0 to 0.6)	.61
Short Form 36 Health Survey score ^d							
Physical Component Summary	5.8 (4.7 to 7.0)	2.8 (1.3 to 4.2)	3.3 (1.3 to 5.2)	18.0 (16.5 to 19.5)	15.7 (13.2 to 18.2)	2.5 (-0.3 to 5.4)	.08
Mental Component Summary	1.2 (-0.2 to 2.6)	-0.7 (-3.0 to 1.6)	2.2 (-0.4 to 4.8)	6.9 (5.1 to 8.7)	3.1 (0.7 to 5.4)	3.6 (0.6 to 6.7)	.02
Categorical outcomes, No. (%) [95% CI]							
Improvement in Oswestry Disability Index score							
≥10 points	119 (66.5) [59.5-73.4]	47 (54.7) [43.9-65.4]	1.3 (1.0-1.6) ^e	148 (94.3) [90.6-97.9]	67 (88.2) [80.7-95.6]	1.1 (1.0-1.1) ^e	.24
≥15 points	97 (54.2) [46.8-61.6]	39 (45.3) [34.6-56.1]	1.2 (0.9-1.6) ^e	145 (92.4) [88.1-96.6]	62 (81.6) [72.7-90.5]	1.1 (1.0-1.3) ^e	.05
≥30 points	48 (26.8) [20.2-33.4]	15 (17.4) [9.3-25.6]	1.7 (1.1-2.9) ^e	111 (70.7) [63.5-77.9]	43 (56.6) [45.2-68.0]	1.3 (1.0-1.6) ^e	.04
≥50%	59 (33.0) [26.0-39.9]	17 (19.8) [11.2-28.4]	1.8 (1.1-2.9) ^e	136 (86.6) [81.2-92.0]	52 (68.4) [57.7-79.1]	1.2 (1.1-1.5) ^e	.01
Improvement in pain numerical rating scale score							
≥2 points	120 (67.0) [60.1-74.0]	57 (64.8) [54.6-75.0]	1.1 (0.9-1.3) ^e	141 (89.8) [85.0-94.6]	66 (85.7) [77.7-93.7]	1.0 (0.9-1.2) ^e	.45
≥3 points	92 (51.4) [44.0-58.8]	45 (51.1) [40.5-61.8]	1.0 (0.8-1.3) ^e	131 (83.4) [77.6-89.3]	60 (77.9) [68.4-87.4]	1.1 (0.9-1.2) ^e	.39
≥5 points	51 (28.4) [21.8-35.2]	23 (26.1) [16.8-35.5]	1.1 (0.8-1.7) ^e	106 (67.5) [60.1-74.9]	44 (57.1) [45.8-68.4]	1.2 (0.9-1.4) ^e	.19
Back surgery, any							
Global patient assessment at least "somewhat better" ^f	147 (82.1) [76-88]	61 (69.3) [60-79]	1.2 (1.0-1.4) ^e	18 (9.9) [5.5-14.3]	8 (9.1) [3.0-15.2]	1.2 (0.5-2.6) ^e	.68
				143 (91.1) [86.6-95.6]	66 (85.7) [77.7-93.7]	1.1 (1.0-1.2) ^e	.30

^a Between-group differences are adjusted for baseline age, sex, race, ethnicity, study site, presence of a positive straight-leg-raise test result at baseline, and elapsed time between symptom onset and randomization.
^b Score range, 0-10; higher scores indicate greater dysfunction.
^c Score range, 0-10; higher scores indicate more pain. Average = pain on average over past 3 days; worst = pain at its worst over past 3 days; least = pain at its (best) over past 3 days.
^d Score range, 0-100; higher scores indicate better physical/mental health status.
^e Data are relative risk (95% CI).
^f Global patient assessment was queried as "How has your leg pain changed since you started taking your study medication?" using the following ordered response categories: very much better, somewhat better, about the same, somewhat worse, much worse, or very much worse.

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Table 3. Adverse Events Reported by Participants Up to the 3-Week Follow-up Visit

Adverse Events ^a	All Participants, No. (%) (n = 267) ^b	Prednisone Group, No. (%) (n = 179) ^c	Placebo Group, No. (%) (n = 88) ^c
Insomnia	55 (15.9)	46 (25.7)	9 (10.2) ^d
Nervousness	40 (11.5)	33 (18.4)	7 (8.0) ^e
Increased appetite	49 (14.1)	40 (22.3)	9 (10.2) ^f
Indigestion	26 (7.5)	20 (11.2)	6 (6.8)
Headache	45 (13.0)	32 (17.9)	13 (14.8)
Joint pain	20 (5.8)	10 (5.6)	10 (11.4)
Sweating	50 (14.4)	35 (19.6)	15 (17.0)
Other	62 (17.9)	46 (25.7)	16 (18.2)
Total reporting ≥1 adverse event	106 (39.7)	88 (49.2)	21 (23.9) ^g

^a Participants could report more than 1 event at a time. All events except "other" were assessed with a questionnaire; events noted as "other" were volunteered by participants.

^b Percentage of all reported adverse events.

^c Percentages of individual adverse events reported in each treatment group.

^d $P = .003$ for prednisone group vs placebo group.

^e $P = .03$ for prednisone group vs placebo group.

^f $P = .02$ for prednisone group vs placebo group.

^g $P < .001$ for prednisone group vs placebo group.

leg pain score. Between-group differences favored the prednisone group, in whom the change was significantly greater at the 3-week visit (Table 2).

Subgroup analyses revealed no statistically significant interactions at either the 3-week or 52-week time points in the between-group changes in the ODI or pain NRS with baseline age, sex, race, ethnicity, elapsed time between onset of symptoms and randomization, lower extremity motor weakness, or presence of a positive straight-leg raise test result.

By the 3-week visit, 88 participants (49.2%) in the prednisone group reported at least 1 adverse event compared with 21 (23.9%) randomized to placebo ($P < .001$). The majority (82.1%) of these were minor, expected adverse effects commonly associated with short courses of prednisone, such as insomnia, nervousness, and increased appetite (Table 3). By the 52-week visit, 208 participants (77.3%) reported a total of 723 adverse events; there were no significant differences in the mean number of adverse events per person in the active- and placebo-treated groups (2.70 vs 2.69; $P = .98$) or in the proportion of participants in each group reporting at least 1 adverse event (80.1% vs 71.6%; $P = .12$). Overall, 5 serious adverse events occurred over the 52-week follow-up period, 3 in the prednisone group (appendectomy, suicide attempt, and deep venous thrombosis) and 2 in the placebo group (upper gastrointestinal tract hemorrhage and partial nephrectomy for renal cell carcinoma); none was judged to be likely due to the study medication.

At the 3-week time point, 130 (74.7%) participants in the prednisone group believed that they had been given the active treatment compared with 48 (52.8%) of placebo-assigned participants ($P = .001$).

Discussion

Acute lumbar radiculopathy associated with a herniated nucleus pulposus commonly causes substantial pain and disability and generates significant costs.^{3,4,32} Treatment options include advice, education, self care, and medica-

tions (including oral steroids), followed by various physical modalities (eg, physical therapy, ultrasound, electrical stimulation), epidural steroids, and microdiscectomy if pain persists.^{3,7,8,33,34}

Over the past 35 years, 6 comparative trials have studied the use of nonepidural steroids in patients with sciatica.³⁵⁻⁴⁰ These trials were generally small with low statistical power (3 enrolled fewer than 40 patients^{36,37,39}). Most of these studies did not find evidence of efficacy of steroid treatment, although 1 recent trial (which enrolled the greatest number of participants) found a trend toward improvement in pain and a significant benefit in function 1 month after a single intramuscular injection of methylprednisolone.⁴⁰ To date, however, no study has examined the effectiveness of a full course of oral steroids in addition to usual care in a well-powered clinical trial.

In this trial of oral prednisone for patients with acute lumbar radiculopathy, we found a small, statistically significant improvement in function (as measured by the ODI) at both 3 weeks and 52 weeks favoring the prednisone-treated group but no difference in lower extremity pain scores at any time point. Several secondary outcomes showed small but inconsistent improvements in the active treatment group relative to the placebo group. Interaction analyses did not reveal any subgroup response that might explain these results. There was no significant difference in the likelihood of undergoing spine surgery up to 52 weeks. While there were significantly more adverse effects in the treatment group noted at 3 weeks, these were primarily transient, expected adverse effects associated with short courses of oral prednisone and there was no difference in adverse events at 1 year; no serious adverse events related to treatment were observed.

The adjusted mean improvement for the primary functional outcome, the ODI, was 6.4 points on a 100-point scale 3 weeks following randomization. This degree of benefit must be interpreted in the context of the clinical setting, as there is no clear consensus regarding the patient-relevant minimum clinically important difference for the ODI, with most published estimates in the range of 5 to 15 points.²¹⁻²⁸

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We designed the study power calculations around a minimum clinically important difference of 7 points, which was chosen to be in the lower end of this interval, although this choice was arbitrary, given the lack of published consensus. Whether the observed improvement in function (without concomitant improvement in pain) merits use of oral steroids for patients with an acute radiculopathy is a difficult decision and, ultimately, becomes a personal one that must be weighed by individual patients and their physicians. In addition, pain may limit function, so as pain decreases, function (ODI) may increase until pain again limits functional capacity. This may explain the improved function without measurable improvement in pain.

Examination of the response curves (Figure 2) for both the ODI and pain NRS show that the small between-group differences observed 3 weeks after randomization were not observed at the 6-week time point. However, between-group differences were statistically significant again at the 52-week follow-up. The magnitude of the difference at the 52-week follow-up is greater than the magnitude of the difference at the 3-week follow-up. We know of no physiological explanation for a potential delayed effect of prednisone. The observed difference at the 52-week follow-up may be due to chance.

An important rationale for using oral steroids is the potential to decrease the need for more invasive interventions.

However, in this trial, the use of prednisone did not decrease the likelihood of undergoing surgery.

Our study had several strengths, including effective randomization, high adherence to the intervention, high follow-up rates, and use of standardized patient-reported outcomes. Several potential limitations should also be noted. While it is possible that allowing up to 3 months after onset of symptoms was too long, we did not find any significant difference in response based on the time to treatment. We chose what we considered to be an adequate dosage for the prednisone treatment, but it may be argued that this dosage was insufficient. Blinding was only partially successful, probably because of the common adverse effects of oral steroids. Although we had multiple secondary outcomes, we did not adjust for multiple comparisons. In addition, generalizability of our results may be limited by the requirement for a positive MRI finding and a baseline ODI score of 30 points or higher.

Conclusions

Among patients with acute radiculopathy due to a herniated lumbar disk, a short course of oral steroids, compared with placebo, resulted in modest improvement in function and no significant improvement in pain.

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Conflict of Interest Disclosures: All authors have completed and submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Dr Carragee reports travel support from the US Army, grants from the Orthopaedic Research and

Education Foundation and AOSpine, and options from Simpirica and Intrinsic Orthopedics. No other disclosures were reported.

Funding/Support: This study was supported by grant R01AR053960 from the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) of the US National Institutes of Health to Drs Goldberg and Avins.

Role of the Funder/Sponsor: NIAMS had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication.

Additional Contributions: We acknowledge the support provided by the following individuals: Nancy E. Wittels, MS, M. Ted Diepenbrock, MS, and Kyaw (Michael) Lin, BA, Kaiser Permanente Northern California, for data acquisition and clinical site management (received salary support from the NIAMS research grant); Cynthia Huynh, RN, Kaiser Permanente Northern California, for data acquisition and quality control (received salary support from the NIAMS research grant); Fiona Sinclair, PA-C, MHS, Kaiser Permanente Northern California, for participant recruitment (received salary support from the NIAMS research grant); and Erika L. Marmalejo, CCRC, Kaiser Permanente Northern California, for regulatory support (received funding from Kaiser Permanente Northern California).

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