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Short-Term Efficacy of Intravenous Pulse Glucocorticoids in Acute Discogenic Sciatica. A Randomized Controlled Trial

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Study Design. Double-blinded randomized controlled trial.

Objective. To test the short-term efficacy of a single intravenous (IV) pulse of glucocorticoids on the symptoms of acute discogenic sciatica.

Summary of Background Data. The use of glucocorticoids in the treatment of acute discogenic sciatica is controversial. A potential advantage of the IV pulse therapy is the ability to distribute high glucocorticoid concentrations to the area surrounding the prolapsed disc without the risks and inconveniences of an epidural injection.

Methods. Patients with acute sciatica (<6-week duration) of radiologically confirmed discogenic origin were randomized to receive either a single IV bolus of 500 mg of methylprednisolone or placebo. Clinical evaluation was performed in a double-blind manner on days 0, 1, 2, 3, 10, and 30. The primary outcome was reduction in sciatic leg pain during the first 3 days following the infusion; secondary outcomes were reduction in low back pain, global pain, functional disability, and signs of radicular irritation. The analysis was performed on an intent-to-treat basis using a longitudinal regression model for repeated measures.

Results. A total of 65 patients were randomized, and 60 completed the treatment and the follow-up assessments. A single IV bolus of glucocorticoids provided significant improvement in sciatic leg pain ($P = 0.04$) within the first 3 days. However, the effect size was small, and the improvement did not persist. IV glucocorticoids had no effect on functional disability or clinical signs of radicular irritation.

Conclusions. Although an IV bolus of glucocorticoids provides a short-term improvement in leg pain in patients with acute discogenic sciatica, its effects are transient and have small magnitude.

Key words: discogenic compression, sciatica, therapy, glucocorticoids. **Spine 2006;31:377–381**

Radicular pain in the lower limbs (sciatica) is common in clinical practice, and an important medical and socioeconomic problem.[1] The prevalence of sciatica is approximately 1.5% in the adult population, and the cumulative lifetime incidence reaches 40%. The herniated disc is generally considered the leading cause of sciatica. The development of disc degeneration is associated with hereditary factors as well as mechanical risk factors.[2,3] The pathophysiology of sciatica includes compression, inflammation, and ischemia of the spinal nerve root by the herniated disc, resulting in ectopic firing, or excessive excitation, by the nerve root.[4,5] Local inflammation (radiculitis) is mediated by metabolic, chemical, and electrophysiologic factors in response to prolapsed disc tissue. Herniated discs contain several inflammatory mediators, such as phospholipase A2, prostaglandin E2, interleukin-1, and tumor necrosis factor-α.[6,7] These substances have induced ectopic firing by the spinal nerve root.[8,9]

A conservative approach, including analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs) and low-stress exercise, is the accepted treatment strategy for acute sciatica.[10] The use of glucocorticoids is still controversial in this indication.[11] Experimental animal studies have shown that glucocorticoids effectively reduce hyperalgesia and excessive excitation in the injured spinal nerve root.[8,12] However, clinical trials of the efficacy of epidural, intramuscular, or oral glucocorticoids in acute sciatica have provided conflicting results.[11] Some trials have shown a short-term advantage,[13,14] while others have not shown any clinical benefit.[11]

A potential advantage of the intravenous (IV) administration as a bolus is the ability to deliver relatively high doses of glucocorticoids in a short time, which could distribute higher glucocorticoid concentrations to the area surrounding the prolapsed disc, without the risks and inconvenience of an epidural injection. Furthermore, it has been suggested that an IV bolus of glucocorticoids has a better risk-benefit ratio than other forms of glucocorticoid administration.[15,16] To our knowledge, IV glucocorticoids have never been critically evaluated in acute sciatica. The purpose of this study was to test the effects of a single IV bolus of glucocorticoid on symptoms of acute discogenic sciatica in a double blind, placebo controlled, randomized trial.

Materials and Methods

Study Design. This is a double blind, randomized controlled, multicenter clinical trial. The study was conducted among the University Hospital of Vaud in Lausanne, the Canton Hospital of Fribourg, and the Regional Hospital of Broye in Switzerland from January 2000 to March 2003. The local ethics committee approved the study protocol. All consecutive patients hospital-

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ized for acute sciatica in these institutions were invited to participate. Patients were eligible if they were older than 16 years and had a first or recurrent episode of sciatica that had lasted for a minimum of 1 week but less than 6 weeks. Up to that point, patients were typically treated conservatively with analgesics, NSAIDs, and physiotherapy.

Sciatica was defined as the presence of pain radiating below the knee, with or without concomitant low back pain, and signs of radicular irritation, such as a positive straight leg raising test (Lasegue test) or a neurologic deficit (motor, sensory, or reflex deficit). Furthermore, the discogenic origin had to be corroborated by computerized tomography or magnetic resonance imaging showing the presence of a herniated disc at a site that corresponds to the clinical presentation. The exclusion criteria were: contraindications to steroids (acute infection, psychiatric comorbidity, unstable diabetes, uncontrolled hypertension, severe heart failure); a major motor impairment or a cauda equina syndrome; a past history of lumbar surgery; a primary lumbar spinal stenosis; pregnancy; inability to read the consent form; or prior treatment for sciatica with glucocorticoids.

Intervention. We randomized the patients after they had signed an informed consent. The hospital pharmacist produced the assignment scheme with a random number generator, and the assignments were kept in sequentially numbered opaque envelopes. Random assignment to the treatment groups was further stratified according to study center.

The patients received a single IV bolus of 500 mg of methylprednisolone (Solu-Medrol®; Upjohn Co., Kalamazoo, MI) or a similar infusion of saline solution 0.9%. The hospitals' pharmacy prepared and a nurse administered the study infusions. The medication codes were kept in sealed envelopes until the end of the study. Patients, nurses, evaluating physicians, and the investigators were blinded to the treatment group assignment. We chose to test a single IV bolus of 500 mg of methylprednisolone because we wished to minimize potential side effects of IV glucocorticoids, while this dose has been shown to have therapeutically relevant antiinflammatory effects.[17,18]

During the duration of the study, all patients received standard care, including analgesics (acetaminophen and/or NSAID and/or tramadol) and physical therapy. During the first 3 days, no concomitant steroid therapy or major analgesics were permitted. After day 3, the treating physician was allowed to use other therapeutic interventions, including glucocorticoids as needed.

Assessment of Outcome. The evaluation was performed on days 0, 1, 2, 3, 10, and 30 in a double-blind manner. A physician performed a standard neurologic examination, and patients completed an evaluation form at the same approximate time at every follow-up visit. Because no data were available on the timing of IV glucocorticoids' effect in sciatica, we selected as our primary endpoint a change in outcome over the first 3 days after the IV pulse, instead of a specific time. The primary outcome was the reduction in sciatic pain during first the 3 days after the IV bolus, measured with a 10-cm visual analog scale (VAS) of sciatic leg pain. VAS of sciatic leg pain was selected as the primary outcome because it is most relevant to the evaluation of sciatica and is sensitive to change in trials.[13,14]

Secondary outcomes were reduction in low back pain (VAS of low back pain), global pain (VAS of global pain and McGill Pain Questionnaire[19]), functional disability (Oswestry questionnaire[20]), and signs of radicular irritation (straight leg raise angle, lumbar flexion [Schober test (cm)]). The 3 visual analog pain scales ranged form 0 (no pain) to 100 (worst pain) and assessed respectively the intensity of leg pain (VAS of leg pain), low back pain (VAS of low back pain), and overall pain (VAS of global pain). Subsequent spine surgery, potential side effects of therapy, concomitant analgesic medication, and additional glucocorticoids, allowed after day 3, were also recorded.

Statistical Analyses. We calculated the sample size based on pilot data and previous published data,[13,21] with the objective of being able to detect a difference of at least 20 mm in the VAS of sciatic leg pain. With a power of 0.80 and an alpha error of less than 0.05, we calculated that at least 60 patients would be needed.

Comparison of the baseline disease characteristics were based on unpaired t tests for continuous normal variables, the Wilcoxon tests for continuous non-normal variables, and the χ^2 test for dichotomous variables. Because measurements of the outcomes were repeated at days 0, 1, 2, 3, 10, and 30, the correlations among these scores needed to be considered in the analysis. We used a mixed model for analysis of repeated measures to compare patterns of change in the different outcome variables between the treatment and placebo groups.[22] Because the primary treatment effect was change in outcomes during the first 3 days after an IV bolus, we used a linear spline regression model with a "knot" at day 3, adjusting for baseline values of the outcome variable. We analyzed the possibility of effect modification by concomitant analgesics or the presence of neurologic deficits by including an interaction term between these variables and treatment allocation.

We also considered whether time as a linear trend or as a quadratic function best fitted the data. Covariates were included in the model only if found to be major confounders or significant predictors of the outcome. All patients who received an initial IV bolus and had at least 1 follow-up evaluation were included in the analysis. Sporadic missing outcomes were assumed to be missing completely at random or missing at random and imputed by the longitudinal regression model. Examining the distribution of the model's residuals validated the multivariate normal assumption for longitudinal analyses. Responders to therapy were predefined as patients who improved their VAS of leg pain by $\geq$20 mm during the first 3 days after the IV bolus. All tests were conducted at an alpha error level of 0.05, 2-sided and performed with SAS software (version 8.1; SAS Institute Inc., Cary, NC) for Windows (Microsoft, Corp., Redmond, WA).

■ Results

A total of 65 patients from 3 centers were randomized, and 60 patients completed the treatment and the follow-up assessments. There were 2 patients who withdrew consent before receiving the IV bolus, and 3 refused subsequent evaluations. No significant difference existed between the 2 treatment groups at baseline (Table 1). As expected, the study population had severe symptomatic sciatica, with high levels of self-reported pain scores, and acute symptoms, with median symptom duration of 15 days. The nerve root involvement (clinical) was also balanced between both groups and was distributed as: 50% of L5, 38% of S1, 8% of L4, and 4% of L3 involvement. Overall, the treatment was well tolerated, with 2 cases of transient hyperglycemia and 1 of facial flush attributable to glucocorticoid infusion.

Table 1. Baseline Characteristics

Disease Characteristics	Glucocorticoid (N = 31)	Placebo (N = 29)	P*
Age (ys)	49.0 (18.3)	45.4 (12.8)	0.39
No. females	14 (45%)	17 (59%)	0.30
Duration of pain (median)	15 days (18)	15 days (19.5)	0.36
Concomitant medications			
NSAID use	8 (26%)	7 (24%)	0.88
Acetaminophen	24 (77%)	23 (79%)	0.86
Tramadol	17 (55%)	18 (62%)	0.57
VAS of leg pain (0–100)	67.1 (22.1)	63.3 (20.7)	0.50
VAS of low back pain (0–100)	47.2 (33.2)	54.6 (31.5)	0.38
VAS of global pain (0–100)	64.9 (20.2)	60.6 (17.6)	0.39
Global pain (0–77)	24.3 (12.1)	21.8 (11.0)	0.40
Neurologic deficits present	16 (52%)	10 (34%)	0.18
Straight leg raise angle	37° (25.7°)	41° (17.1°)	0.46
Lumbar flexion	2.4 cm (1.46)	2.6 cm (1.26)	0.55
Functional disability (0–100)	26.7 (7.9)	26.7 (7.5)	0.98

Unless indicated otherwise, all values are expressed as mean ± standard deviation. When not normally distributed, variable's medians and interquartile ranges are reported.
*The *t* test for normally distributed continuous variables, Wilcoxon test for non-normally distributed variables, and χ^2 test for dichotomous variables.
Functional disability indicates Oswestry Low Back Pain Disability Questionnaire ranging from 0 (no disability) to 100 (worst disability); Global pain, McGill pain-rating index ranging from 0 to 77, and higher scores indicate more pain; Lumbar flexion (Schober test), difference in distance between the supine position (5 cm) and full lumbar flexion; Straight leg raise angle (Lasegue angle), straight leg raise angle causing severe sciatic pain.

The slope of the patients' evaluation of leg pain (VAS of leg pain) over the duration of the study was significantly different between the 2 treatment groups during the first 3 days ($P = 0.04$), with a sharper decline in pain during day 1 in the glucocorticoid group followed by a small rebound (Figure 1). After day 3, the evolution of leg pain was similar in both groups ($P = 0.22$). Although the difference in sciatic pain improvement is significant between the 2 treatment groups, mean effect size was small, with only a 5.7 mm (95% confidence interval 0.3–10.9) more VAS of sciatic leg pain reduction in the glucocorticoids group at day 1. Furthermore, the beneficial symptomatic effect of IV glucocorticoids was transient (about 2 days) and followed by a small rebound in leg pain. Overall, pain levels improved substantially in both groups during the first 10 days. The proportion of responders (decrease in VAS ≥20 mm) at day 1 was 48% (15 patients) in the glucocorticoid group compared to 28% (8 patients) in the placebo group ($P = 0.097$). No effect modification by concomitant analgesics, NSAIDs, or the presence of neurologic deficits was apparent.

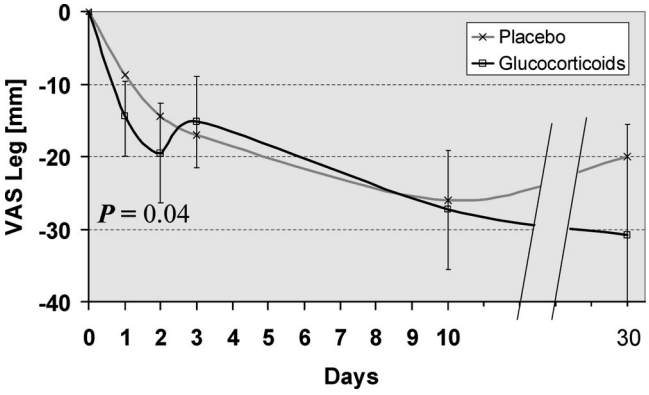

Figure 1. Evolution of leg pain (primary outcome) after treatment. Evolution of sciatic leg pain measured with a 10-cm VAS (VAS of sciatic leg pain) ranging from 0 (no pain) to 100 (worst pain) after an IV bolus of glucocorticoids (-■-) or placebo (-⁎-). (Evolution after day 10 not represented.) Vertical lines represent 95% confidence intervals. Results were adjusted for baseline levels of the VAS of leg pain. The *P* value corresponds to the analysis of the pattern of change in the VAS of leg pain between treatment groups over the first 3 days.

None of the secondary outcomes was significantly different between the 2 groups at any follow-up point, and both groups showed a similar significant decline in symptoms. Although the evolution of these outcomes tended to be more favorable for the glucocorticoid group during the first 3 days, neither the improvement in low back pain (VAS of low back pain, $P = 0.73$), global pain (VAS of global pain, $P = 0.09$; McGill questionnaire, $P = 0.94$), straight leg raise angle ($P = 0.80$), lumbar flexion (Schober test, $P = 0.58$), nor functional disability (Oswestry questionnaire, $P = 0.53$) was significantly better with glucocorticoids than placebo. Furthermore, no significant difference was observed in the proportion of patients requiring spine surgery within the first month (placebo 1 (1.7%), glucorticoids 3 (5%), $P = 0.61$), in analgesic use (acetaminophen, $P = 0.90$; tramadol, $P = 0.75$; NSAID, $P = 0.29$), or in subsequent glucocorticoid use ($P = 0.65$) during follow-up.

■ Discussion

To our knowledge, this is the first trial of an IV bolus of glucocorticoids (500-mg methylprednisolone) in acute discogenic sciatica. We found a significant short-term improvement of sciatic pain (VAS of sciatic leg pain, $P = 0.04$) with glucocorticoids followed by a small rebound. However, mean effect size in pain reduction was small and lasted only about 2 days. Approximately half the patients in the glucocorticoid group (48%) had a clinically relevant response (decline in VAS of leg pain ≥20 mm) at day 1 compared to 28% in the placebo group ($P = 0.097$). No other secondary outcomes such as lumbar pain, global pain, straight leg raise angle, lumbar flexion, or functional disability were significantly improved by the glucocorticoid treatment. As expected, no durable benefit was observed at day 30 with a single IV bolus of glucocorticoids for any outcome. The transient benefit and small effect size of IV glucocorticoids on symptoms of acute sciatica probably do not warrant a large clinical use in this indication.

Our results are consistent with previous studies of epidural glucocorticoid injections in acute sciatica, which have suggested that its benefits are short-term and of small magnitude.[11] In particular, 2 recent studies showed a small but significant reduction in leg pain between weeks 2 and 6 with epidural glucocorticoid injections.[13,14] The longer duration of the effect of epidural compared to IV glucocorticoids injections is probably explained by the different pharmacokinetic properties of the

glucocorticoids used. The efficacy of oral or intramuscular glucocorticoid administration has been less studied[23–26] but also only suggested a short-term benefit, if any.

Acute sciatica is a heterogeneous condition,[27] resulting from diverse pathophysiologic mechanism, which could explain why some patients respond while others do not seem to benefit at all from glucocorticoids. It is conceivable that patients who respond to a single IV bolus of glucocorticoids (approximately 50%) are also those who benefit from longer courses of glucocorticoids. A "test dose" might allow to limit the prescription of potentially harmful therapies to only those patients most likely to benefit from them. Further research would be needed to establish whether IV steroids can be used as a "therapeutic test" to select subgroups of patients most likely to benefit from an extended glucocorticoid therapy or epidural injection.

Some potential limitations need discussion. First, although this study had sufficient power to detect meaningful changes in leg pain, the study's primary outcome, the number may have been inadequate to show change in secondary outcomes. Furthermore, in health conditions with rapid spontaneous improvement such as acute discogenic sciatica, showing therapeutic efficacy is hindered by regression to the mean. Second, we had insufficient power to analyze reliably the effect of glucocorticoids in specific subgroups, such as different types of disc herniation or sciatica with neurologic deficits. Third, unblinding might have occurred as a result of transient glucocorticoid side effects, such as flushing, hypertension, or hyperglycemia. However, these side effects were noted in only 3 patients (1 with flushing and 2 with hyperglycemia) and are unlikely to have affected much of the patients' self-reported evaluation of symptoms because they did not necessarily associate them with their treatment. Finally, we have restricted the inclusion to patients presenting with radiologically confirmed severe sciatica, a group that was judged to have symptoms not responding to outpatient treatment and to warrant hospitalization. Therefore, the results of this study can only be generalized to patients with severe acute discogenic sciatica.

In conclusion, we found that a single IV pulse of glucocorticoids provides a small and transient improvement in sciatic leg pain, and no effect on functioning or objective signs of radicular irritation. Future research will need to determine if such a short-term effect is clinically useful to identify a subgroup of patients that respond to glucocorticoids.

■ Key Points

- A single IV bolus of glucocorticoids provides significant short-term improvement in sciatic leg pain.
- The effect size of this improvement is relatively small and transient.
- An IV bolus of glucocorticoids had no effect on functioning or objective signs of radicular irritation.

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References

1. Frymoyer JW. Back pain and sciatica. *N Engl J Med* 1988;318:291–300.
2. Battie MC, Videman T, Gibbons LE, et al. 1995 Volvo Award in clinical sciences. Determinants of lumbar disc degeneration. A study relating lifetime exposures and magnetic resonance imaging findings in identical twins. *Spine* 1995;20:2601–12.
3. Richardson JK, Chung T, Schultz JS, et al. A familial predisposition toward lumbar disc injury. *Spine* 1997;22:1487–92.
4. Olmarker K, Holm S, Rosenqvist AL, et al. Experimental nerve root compression. A model of acute, graded compression of the porcine cauda equina and an analysis of neural and vascular anatomy. *Spine* 1991;16:61–9.
5. Ozaktay AC, Kallakuri S, Cavanaugh JM. Phospholipase A2 sensitivity of the dorsal root and dorsal root ganglion. *Spine* 1998;23:1297–306.
6. Takahashi H, Suguro T, Okazima Y, et al. Inflammatory cytokines in the herniated disc of the lumbar spine. *Spine* 1996;21:218–24.
7. Willburger RE, Wittenberg RH. Prostaglandin release from lumbar disc and facet joint tissue. *Spine* 1994;19:2068–70.
8. Muramoto T, Atsuta Y, Iwahara T, et al. The action of prostaglandin E2 and triamcinolone acetonide on the firing activity of lumbar nerve roots. *Int Orthop* 1997;21:172–5.
9. Ozaktay AC, Cavanaugh JM, Asik I, et al. Dorsal root sensitivity to interleukin-1 beta, interleukin-6 and tumor necrosis factor in rats. *Eur Spine J* 2002;11:467–75.
10. Bigos S, Bowyer O, Brean G. *Acute Low Back Problems in Adults. Clinical Practice Guideline*. AHCPR Publications Clearinghouse ed. Washington, DC: US Government Printing Office; 1994.
11. Koes BW, Scholten RJ, Mens JM, et al. Efficacy of epidural steroid injections for low-back pain and sciatica: A systematic review of randomized clinical trials. *Pain* 1995;63:279–88.
12. Hayashi N, Weinstein JN, Meller ST, et al. The effect of epidural injection of betamethasone or bupivacaine in a rat model of lumbar radiculopathy. *Spine* 1998;23:877–85.
13. Carette S, Leclaire R, Marcoux S, et al. Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997;336:1634–40.
14. Karppinen J, Malmivaara A, Kurunlahti M, et al. Periradicular infiltration for sciatica: A randomized controlled trial. *Spine* 2001;26:1059–67.
15. Imbasciati E, Gusmano R, Edefonti A, et al. Controlled trial of methylprednisolone pulses and low dose oral prednisone for the minimal change nephrotic syndrome. *Br Med J (Clin Res Ed)* 1985;291:1305–8.
16. Picco P, Gattorno M, Buoncompagni A, et al. 6-methylprednisolone 'mini-pulses': A new modality of glucocorticoid treatment in systemic onset juvenile chronic arthritis. *Scand J Rheumatol* 1996;25:24–7.
17. Droogan AG, Crockard AD, McMillan SA, et al. Effects of intravenous methylprednisolone therapy on leukocyte and soluble adhesion molecule expression in MS. *Neurology* 1998;50:224–9.
18. Roujeau JC. Pulse glucocorticoid therapy. The 'big shot' revisited. *Arch Dermatol* 1996;132:1499–502.
19. Melzack R. The McGill Pain Questionnaire: Major properties and scoring methods. *Pain* 1975;1:277–99.
20. Fairbank JC, Couper J, Davies JB, et al. The Oswestry low back pain disability questionnaire. *Physiotherapy* 1980;66:271–3.
21. Zuffrey P, Guerne P, Vischer T. Effectiveness of IV bolus of methylprednisolone on radicular pain in patients with acute sciatalgias. Prospective study of 10 patients, [French]. Poster presented at the Annual Meeting of the French Society of Rheumatology. Paris; 1998.
22. Skrondal A, Rabe-Hesketh S. *Generalized Latent Variable Modeling: Multilevel, Longitudinal and Structural Equation Models*. Boca Raton, FL: Chapman & Hall/CRC; 2004.
23. Haimovic IC, Beresford HR. Dexamethasone is not superior to placebo for treating lumbosacral radicular pain. *Neurology* 1986;36:1593–4.
24. Kwasucki J, Olbrych-Karpinska B, Stepien A, et al. Assessment of dexameth-

asone effectiveness in the treatment of ischalgia [in Polish]. *Neurol Neurochir Pol* 1993;27:515–22.
25. Porsman O, Friis H. Prolapsed lumbar disc treated with intramuscularly administered dexamethasone phosphate. A prospectively planned, double-blind, controlled clinical trial in 52 patients. *Scand J Rheumatol* 1979;8:142–4.
26. Hedeboe J, Buhl M, Ramsing P. Effects of using dexamethasone and placebo in the treatment of prolapsed lumbar disc. *Acta Neurol Scand* 1982;65:6–10.
27. Weinstein SM, Herring SA, Derby R. Contemporary concepts in spine care. Epidural steroid injections. *Spine* 1995;20:1842–6.