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Efficacy of Epidural Perineural Injections With Autologous Conditioned Serum for Lumbar Radicular Compression

An Investigator-Initiated, Prospective, Double-Blind, Reference-Controlled Study

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Study Design. Prospective, double-blind, reference-controlled, investigator-initiated, single center.

Objective. To evaluate the efficacy of Autologous Conditioned Serum (ACS; Orthokine) for the treatment of lumbar radicular compression in comparison to triamcinolone.

Summary of Background Data. Evidence from animal studies indicates that cytokines such as interleukin-1 play a decisive role in the pathophysiology of lumbar radiculopathy. ACS is enriched in the interleukin-1 receptor antagonist and other anti-inflammatory cytokines.

Methods. Thirty-two patients were treated by epidural perineural injections with ACS; 27 patients were treated with 5 mg triamcinolone and 25 patients with 10 mg triamcinolone. Treatment was applied once per week for 3 consecutive weeks and followed for 6 months. The Visual Analogue Scale (VAS) of low back pain was the primary outcome measure. The Oswestry Disability Index (ODI) was the secondary endpoint of the study. All statistical analyses were performed in an exploratory manner using SAS for Windows, version 8.2, on a personal computer. Descriptive statistics were calculated for the VAS and ODI by treatment group and time point. The data were submitted to a repeated-measurements analysis of variance with effects on treatment group, time, and treatment group-by-time interaction.

Results. Patients with lumbar back pain who were treated with ACS or the 2 triamcinolone concentrations showed a clinically remarkable and statistically significant reduction in pain and disability, as measured by patient administered outcome measurements. From Week 12 to the final evaluation at Week 22, injections with ACS showed a consistent pattern of superiority over both triamcinolone groups with regard to the VAS score for pain, but statistical significance was observed only at Week 22 in direct comparison to the triamcinolone 5 group. However, there was no statistically significant difference between the 2 triamcinolone dosages during the 6 months of the study.

Conclusion. ACS is an encouraging treatment option for patients with unilateral lumbar radicular compression. The decrease in pain was pronounced, clinically remarkable, and potentially superior to steroid injection.

Key words: cytokine, interleukin-1 receptor antagonist, low back pain, autologous conditioned serum, Orthokine, steroid injection, lumbar radicular compression, VAS, Oswestry Disability Index. **Spine 2007;32:1803–1808**

Mechanical compression of lumbar nerve roots by the protruded or herniated nucleus pulposus has been regarded as a major cause of low back pain. However, during the past decade, the important role of inflammation of the nerve roots in this disease has become better appreciated. Cytokines like interleukin-1 (IL-1) have been identified as pivotal mediators of inflammatory and degenerative changes affecting the elements of the musculoskeletal system, including the lumbar spine.[1]

Various strategies for inhibiting the biologic activities of IL-1 have been developed. In particular, the IL-1 receptor antagonist (IL-1Ra), a naturally occurring inhibitor of IL-1, has been discovered.[2–4] This 25-kDa glycoprotein is produced by macrophages and certain additional types of cells. It binds to the type I IL-1 receptor without initiating signal transduction, thereby blocking the biologic actions of IL-1.[5]

The efficacy of human recombinant IL-1Ra in treating rats with experimental allergic radiculitis has been assessed by comparison to prednisolone and saline.[6] Compared with saline, both treatments improved signs and symptoms of experimental polyradiculoneuropathy. Prednisolone appeared slightly more effective than IL-1Ra.

Recently, human recombinant IL-1Ra has obtained regulatory approval in the United States and Europe for the treatment of intractable rheumatoid arthritis when combined with methotrexate. Extensive Phase III clinical studies and postmarketing surveillance have confirmed the safety and effectiveness of recombinant IL-1Ra in humans.[7]

Stimulation of the endogenous production of IL-1Ra is an alternative approach to the delivery of recombinant protein. A method for increasing the autologous production of human IL-1Ra by whole venous blood has been recently described.[8] According to this method, venous blood is drawn into syringes containing $CrSO_4$-treated glass beads. Following an incubation of 24 hours, serum is enriched in IL-1Ra by a factor of about 140 in com-

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parison to baseline values. This increase is comparable to the one observed in cultures of purified monocytes exposed to IgG. There is no induction of IL-1β or tumor necrosis factor (TNF)-α. In addition, incubation with glass beads for 24 hours does not lead to extensive cell death, hemolysis is mild and not clinically remarkable, and the major serum protein composition is not affected. This IL-1Ra-enriched, Autologous Conditioned Serum (ACS) is injected into the affected area, *e.g.*, spine or knee joint, of the recipient. Based on the above principles, a medical device has been developed and marketed as Orthokine. The product has a worldwide CE-mark.

In order to explore the potential therapeutic benefit of ACS under controlled conditions, a prospective, randomized, patient- and observer-blind, reference-controlled, single-center study was performed with patients with lumbar radicular compression. Triamcinolone was used as the comparator/reference therapy. The observation period was 6 months. The study addressed the following questions:

1. Is ACS (Orthokine) effective in the treatment of symptoms?
2. How does ACS compare to triamcinolone, given at a standard dose (10 mg) and low dose (5 mg)?
3. Is there any longer-term benefit from these short-term treatments?

■ Patients and Methods

This investigator-initiated study was conducted in compliance with the German Drug Law. The ethical review committee of the medical faculty at the University of Bochum approved the study protocol.

Consecutive male and female outpatients with unilateral lumbar radicular compression as a critical inclusion criterion and willing to participate were enrolled into the study. Patients provided a written informed consent. The clinical diagnosis was confirmed by magnetic resonance imaging or computerized tomography showing a herniation of the nucleus pulposus or scarring after previous surgery. Pain duration was at least 6 weeks, and pain intensity was moderate to severe.

Patients needing early surgery because of clinically remarkable pareses or unbearable pain were excluded from the study. Other critical exclusion criteria comprised additional neurologic illnesses, cervical myopathy, systemic bone or joint illnesses, previous epidural or epidural perineural injection to the affected nerve root in the last 3 months, and cortisone or opioid use in the last 6 months.

All pain medications were discontinued at the beginning of the trial; patients received no additional medical therapy or physiotherapy. At the request of the ethical review board, ibuprofen was allowed for the treatment of pain during the 6-month trial period.

The average dosage of ibuprofen was 1200 mg per day, and there was no significant different usage between the 3 groups. None of the patients had ibuprofen-induced side effects.

According to the protocol, 60 patients were to be included (20/study arm). In total, 90 patients were recruited. Patients were randomized to 1 of the 3 groups and received 3 epidural perineural injections of ACS, 10 mg triamcinolone, or 5 mg triamcinolone (Table 1). The unit of randomization was the individual patient. Allocation was made by opening sequentially numbered sealed envelopes. These had been filled by a study nurse not involved in the care of the patients using a random number table. There were 2 dropouts; these patients refused further injections. Four additional patients were excluded because of missing data. A total of 84 patients were evaluated.

ACS was produced as described by Meijer *et al.*[8] All injections were performed under radiograph control.[9] Patients and the responsible physicians were blinded. For technical reasons, blinding was not possible for the injection procedure. This was performed by a physician not otherwise involved in the care of the study subjects.

Interventions were carried out in an orthopedic practice in close cooperation with the orthopedic department of the medical faculty (University of Bochum, Bochum, Germany). Following a run-in period of 2 weeks, necessary for the preparation of ACS, patients were injected once per week for 3 consecutive weeks (time points 1, 2, and 3). Follow-up examinations were scheduled at 6 weeks (time point 4), 10 weeks (time point 5), and 22 weeks (time point 6) following the first injection.

Before receiving the first injection and at the follow-up visits, patients documented their pain intensity using the 100 mm Visual Analogue Scale (VAS), ranging from 0 (pain free) to 100 (greatest pain intensity). This assessment was the primary endpoint of the study. The secondary endpoint was the Oswestry Disability Index (ODI) at selected time points. Both methods of assessment are well known and accepted outcome scores for low back pain.[10–12]

Using the epidural perineural injection with a double-needle technique, it is possible to infiltrate selective 1 nerve root. An oblique interlaminar approach with a 29-G spinal needle leads into the anterior epidural space and reaches the nerve root directly. Therefore, only a small amount of medication is necessary, in former studies 1 m^3 local anesthetic plus 10 mg triamcinolone proved to be sufficient. This technique had better outcome than paravertebral injections, adverse side effects are lower than with the conventional technique, and injections can also be performed on outpatients.[9]

Table 1. Study Design and Data Assessment Points

	Total Time (wk)							
	0	1	2	3	4	8	12	24
Injections			1st injection	2nd injection	3rd injection			
Time after 1st injection (wk)						6	10	22
Time point	1st investigation 0 (baseline)		1	2	3	1st follow-up 4	2nd follow-up 5	3rd follow-up 6

The injected material was 1 m^3 local anesthetic plus 10 mg triamcinolone in the first group, 1 m^3 local anesthetic plus 5 mg triamcinolone in the second group, and the conditioned autologous serum only in the third group, no other medications have been added.

The selection of the sample size was pragmatic for this exploratory study. All statistical analyses were performed in an exploratory manner. Statistical analysis was performed using SAS for Windows, version 8.2, on a personal computer. Descriptive statistics (n, mean, standard deviation, median, lower and upper quartiles, minimum and maximum) were calculated for the VAS and ODI score by treatment group (Groups 1–3 and the total) and time point, including the last time point with available data. Descriptive statistics were also calculated for the difference in VAS and ODI score to the first time point.

The data were submitted to a repeated-measures analysis of variance with effects on treatment group, time, and treatment group-by-time interaction. The differences between treatment groups were examined for score at time point 1, score at last time point 6, score difference last time point minus time point 1, using separate analyses of variance with "treatment group" included in the model. From these analyses, 95% confidence intervals for the differences between the treatment groups were calculated. Time profiles were then analyzed per treatment group using analysis of variance with effects for subject and time included in the model. Assumptions for analysis of variance appear to hold from inspection of the data distributions and the residuals plots.

■ Results

Study Subjects

A total of 84 patients, 52 men and 32 women, were evaluated. Of these, 83 patients had complete time courses for VAS and ODI. One patient, in the 10-mg triamcinolone group, provided no VAS or ODI data for time point 6.

The mean age was 53.9 years, ranging from 29 to 81 years. At baseline, there was no statistically significant difference between the groups with respect to age, sex, duration of symptoms, and causes of compression signs (*e.g.*, herniated disc, protrusion, spinal stenosis, scars). The use of ibuprofen did not differ between groups.

Thirty-two patients were treated by epidural perineural injections of ACS, 27 were injected with 5 mg triamcinolone, and 25 received 10 mg triamcinolone.

Results for the Primary Study Endpoint

The pain intensity scores and the time curves for VAS are shown in Figure 1; mean, SD, and median values are given.

The 3 treatment groups were found to be comparable with regard to VAS at baseline ($P = 0.44$) showing mean values of 78, 82, and 85 for ACS, triamcinolone 5 mg, and triamcinolone 10 mg, respectively (analysis of variance). Pain intensity was high initially but began to decline even after the first injection, irrespective of treatment. A further decrease in pain was observed in all groups up to Week 4 after the third injection (Week 6 after the first injection).

All comparisons within each treatment group were found to be statistically significant ($P < 0.001$ in all cases) in the framework of ordered testing (*i.e.*, from time point 6 down to time point 2). VAS already showed a statistically significant reduction in all treatment groups from time point 1 to 2. VAS at time points 4, 5, and 6 appeared similar in the 2 triamcinolone groups. A further reduction of VAS from time point 4 to 5 was only observed in the ACS group ($P = 0.002$).

There was no significant difference between the 3 groups at the beginning of treatment, but at the end of the observation period.

The most pronounced pairwise difference was found between ACS and triamcinolone 5 mg (mean, −13.5 in favor of ACS, $P = 0.06$) (Table 2). It is to be noted that the mean value for VAS in the ACS group (23.3) markedly differed from the median (12.5), indicating a skewed data distribution. Thus, application of the nonparametric Kruskal-Wallis test was considered as more appropri-

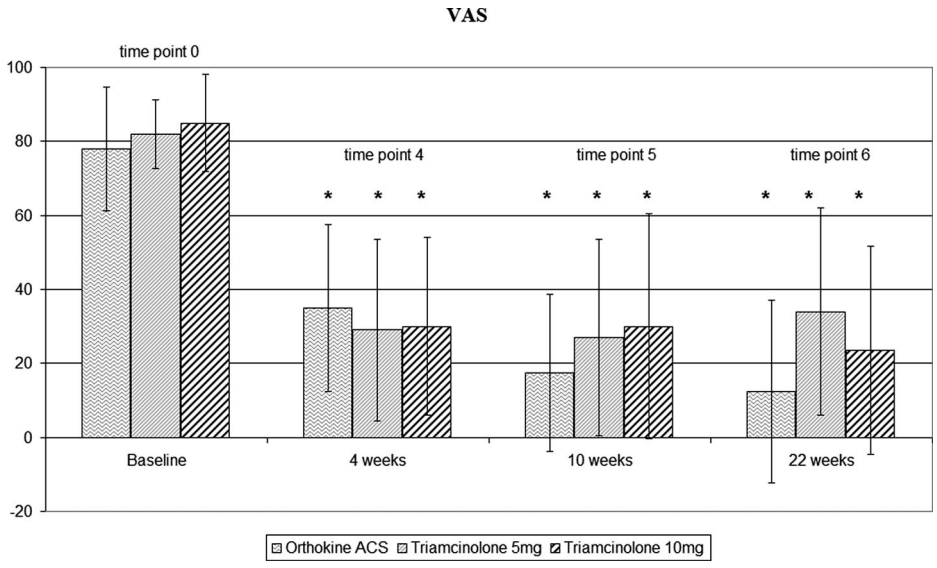

Figure 1. Results for the primary study endpoint. The pain intensity scores and the time curves for VAS are shown. Mean, SD, and median are given. *Significant difference from baseline. Time schedule is given in weeks after the first injection.

Table 2. Pairwise Comparisons of Treatment Groups and VAS at End of Observation

Comparison	Mean Difference	95% CI
ACS − 5 mg triamcinolone	−13.5	(−27.4, 0.4)
ACS − 10 mg triamcinolone	−9.3	(−23.5, 4.9)
5 mg − 10 mg triamcinolone	4.2	(−10.6, 19.0)

ate. At nominal significance level ($\alpha = 5\%$; 2-sided), the ACS group was found statistically significantly different from triamcinolone 5 mg with regard to VAS at the end of the study ($P = 0.046$).

Secondary Study Endpoint

The ODI results are shown in Table 3; mean, SD, and median values are given.

The 3 treatment groups were found to be comparable with regard to baseline values ($P = 0.54$) showing mean values of 22, 21, and 19 for ACS, triamcinolone 5 mg and triamcinolone 10 mg, respectively (analysis of variance). The ODI improved considerably following treatment. All comparisons within each treatment group were found to be statistically significant ($P < 0.001$ in all cases) in the framework of ordered testing (*i.e.*, from time point 6 down to time point 4). This means that the ODI was already statistically significantly reduced in all treatment groups at time point 4, *i.e.*, the first measurement after time point 1. ODI at time points 4, 5, and 6 appeared similar in the 2 triamcinolone groups. A further reduction of ODI from time point 4 to 5 was only observed in the ACS group ($P = 0.03$). At time point 6, the ODI was similar in all treatment groups. The difference between the 3 groups was not statistically significant ($P = 0.95$ for score at end, $P = 0.74$ for the reduction).

All 3 treatments were well tolerated. There were no serious adverse events. Three patients, 1 from each group, complained about severe headache after the injection. This adverse effect was attributed to the injection procedure.

■ Discussion

This double-blind, randomized, reference-controlled, exploratory study in patients with unilateral lumbar radicular compression was undertaken to address the 3 issues listed in the introduction.

Regarding the efficacy of ACS, following 3 repeated epidural perineural injections at weekly intervals, both the primary efficacy measure (VAS) as well as the secondary endpoint (ODI) showed a statistically significant reduction of pain and disability compared with the baseline. Thus, ACS was effective in the treatment of symptoms caused by lumbar radicular compression.

Epidural perineural triamcinolone (as reference therapy) given as a 10-mg or 5-mg dose also reduced pain and disability. Comparisons to baseline showed a statistically significant effect. However, there was no statistically significant difference between the 2 triamcinolone dosages during the 6 months of the study.

From Week 12 to the final evaluation at Week 26, injections with ACS showed a consistent pattern of superiority over both triamcinolone groups with regard to the primary outcome measurement (VAS score for pain), but statistical significance was observed only at Week 26 in direct comparison to the triamcinolone 5 group in favor of ACS. There was no statistically significant difference between all groups with respect to the ODI.

The trial duration was 6 months, and the last assessment was performed at Week 22 after the first injection. Over the entire observation period, ACS and triamcinolone effectively, and with statistical significance, suppressed both pain and disability. There was a clear indication that ACS was superior to triamcinolone in the long-term reduction of pain.

Our data bear comparison with other, related clinical trials in the literature. When interpreting the results of this exploratory study, it has to be taken into account that patients needing early surgery because of clinical pareses or unbearable pain were excluded. This is a difference from the study of steroid injection described by Wilson-MacDonald *et al*,[13] which enrolled 93 patients who had been categorized as potential candidates for surgery. The mean ODI at baseline was about 40 as opposed to about 20 in the current study. Their study[13] demonstrated a significant reduction in pain early on in those patients having an epidural injection of methylprednisolone as opposed to patients having an intramuscular injection ($P < 0.004$). This observation thus supports epidural intervention, at least with respect to pain relief.

As an alternative to steroids, there is evidence that TNF-α injections are also effective. Korhonen *et al*[14] en-

Table 3. Secondary Study Endpoint

Therapy	Time Point 1: Baseline	Time Point 4: 6 Weeks	Time Point 5: 10 Weeks	Time Point 6: 22 Weeks
ACS [mean (SD)]	22.0 (8.3)	13.8 (9.8)	11.2 (10.2)	11.7 (9.2)
Median	23.5	13.0	8.0	10.0
5 mg triamcinolone [mean (SD)]	20.6 (8.1)	12.1 (9.0)	12.4 (9.0)	11.1 (7.1)
Median	19.0	9.0	10.0	10.0
10 mg triamcinolone [mean (SD)]	19.4 (9.9)	11.0 (9.5)	11.0 (10.2)	11.4 (10.3)
Median	19.0	10.0	9.0	9.5

The Oswestry Disability Index (ODI) results in the three treatment groups. Mean (SD) values are given. There was no significant difference between the groups at any time.

Table 4. Comparison to Literature Results

Reference	Therapy	VAS Baseline	VAS at End of Observation	ODI Baseline	ODI at End of Observation
Current study	ACS	77.8 ± 16.4	23.3 ± 24.8*	22.0 ± 8.3	11.7 ± 9.2
	Triamcinolone 5 mg	81.9 ± 8.7	36.8 ± 28.3	20.6 ± 8.1	11.1 ± 7.1
	Triamcinolone 10 mg	84.8 ± 12.4	32.6 ± 28.2	19.4 ± 9.9	11.4 ± 10.3
Karppinen	Infliximab	76.0 ± 18	16 ± 18	43 ± 21	7 ± 6
Genevay	Etanercept	36.4 ± 39.8	7 ± 10.8	75.4 ± 19.4	17.3 ± 13.1

Data are mean ± SD.
*Median = 12.5.

rolled 10 patients with disc herniation-induced severe sciatica and used the need for early surgery as one endpoint of a study that examined the efficacy of infliximab, a monoclonal antibody against TNF-α. The differences significantly favored infliximab treatment.

Genevay *et al*[15] investigated 10 patients admitted to hospital with acute severe sciatica and showed sustained improvement after a short treatment with etanercept, another TNF-α inhibitor. Both of these studies used historical controls for comparison.

Despite differences in study objectives and patient characteristics, it is possible to compare their results to those of the current study (Table 4).

As shown in Table 4, ACS and infliximab have a roughly comparable strong effect on pain as shown by VAS at baseline and at the end of the observation period. When looking at the results for triamcinolone, it may be speculated that the effect of ACS and infliximab is clinically superior to steroid injection. ACS and infliximab act at 2 different molecular targets directly involved in nerve root inflammation.[16] It would be interesting to explore the relative contribution of IL-1 and TNF-α in nerve root inflammation and differential therapeutic options based on these different principles.

Potential complications of the epidural perineural injection technique are seldom, indeed lower and less severe than in conventional techniques, and are implicating postinjectional headaches because of inadvertent dura puncture. ACS is an autologous serum with no side effects. In comparison, the most common side effects of infliximab are upper respiratory tract infections, urinary tract infections, cough, rash, back pain, nausea, vomiting, abdominal pain, headache, weakness, and fever. Often an allergy to this drug occurs, and decreased white and red blood cell and decreased platelet counts and vasculitis have been reported with infliximab. Infections have been reported during treatment with infliximab, and it should be discontinued if a serious infection develops during treatment. Before starting infliximab, persons are recommended to have tuberculosis skin testing (PPD tests for TB) because of reports of reactivation of tuberculosis in patients taking infliximab. In controlled studies of TNF-α-blocking agents, including infliximab, more cases of lymphoma and other malignancies have been observed among patients receiving the agents than among control group patients. Therefore, ACS has potential benefits over infliximab in the mentioned cases.

The comparison between our own results and the effects of etanercept is difficult because the VAS at baseline in the etanercept study was low and patients seemed to suffer more from subjective disability than pain. The degree of disability was considerably lower in the current study compared with those described in the references.[13–15] It is interesting to note that chronic or acute pain does not necessarily correlate with the degree of disability across studies. According to a meta-analysis,[17] the mean ODI baseline values in the current study are representative for patients with primary back pain or spondylolisthesis. Mean values around 40 are observed in patients with chronic back pain, sciatica, or fibromyalgia. Although ACS showed a remarkable improvement of subjective disability, it would be interesting to examine its effect in patients with a higher degree of disability.

The average costs for an ACS therapy of a patient is about 1000€ for a 6-month treatment and has to be taken into account if we discuss new therapies. We know that, in some special cases, insurance carriers did already pay for this kind of therapy.

But besides all economic considerations, which always play an important role, ACS is shown to be an elegant and useful tool for the treatment of lumbar radicular compression.

■ Conclusion

Autologous Conditioned Serum (Orthokine; ACS) is a promising, new treatment option for patients with unilateral lumbar radicular compression. The decrease in pain was pronounced, significant, and potentially superior to steroid injection.

■ Key Points

- Epidural perineural ACS is an encouraging treatment option for patients with unilateral lumbar radicular compression.
- Epidural perineural triamcinolone given as a 10 mg or 5 mg dose statistically significant reduces pain and disability in patients with unilateral lumbar radicular compression.
- There is no statistically significant difference between epidural perineural triamcinolone given as a 10-mg or 5-mg dose in patients with unilateral lumbar radicular compression.

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