Intramuscular Oxygen-Ozone Therapy in the Treatment of Acute Back Pain With Lumbar Disc Herniation

A Multicenter, Randomized, Double-Blind, Clinical Trial of Active and Simulated Lumbar Paravertebral Injection

Marco Paoloni, MD,*† Luca Di Sante, MD,*† Angelo Caccio, MD,† Dario Apuzzo, MD,† Salvatore Marotta, MD,† Michele Razzano, MD,† Marianno Franzini, MD,§ and Valter Santilli, MD*†

Study Design. Multicenter randomized, double-blind, simulated therapy-controlled trial in a cohort of patients with acute low back pain (LBP) due to lumbar disc herniation (LDH).

Objective. To assess the benefit of intramuscular-paravertebral injections of an oxygen-ozone (O₂O₃) mixture.

Summary of Background Data. Recent findings have shown that O₂O₃ therapy can be used to treat LDH that fails to respond to conservative management. However, these findings are based on intradiscal/intraforaminal O₂O₃ injection, whereas intramuscular-paravertebral injection is the technique used most in clinical practice in Italy and other Western countries.

Methods. Sixty patients suffering from acute LBP caused by LDH was randomized to an intramuscular O₂O₃ or control group. Patients were observed up to assess pain intensity, LBP-related disability, and drug intake (15 [V2] and 30 [V3] days after treatment started, and 2 weeks [V4], and 3 [V5] and 6 [V6] months after treatment ended).

Results. A significant difference between the 2 groups in the percentage of cases who had become pain-free (61% vs. 33%, P < 0.05) was observed at V6. Patients who received O₂O₃ had a lower mean pain score than patients who received simulated therapy throughout the observation period. A significant improvement was observed in LBP-related disability in the study group patients when compared with the control group patients. Active O₂O₃ therapy was followed by a significantly lower number of days on nonsteroidal anti-inflammatory drugs at V2 and V3 and by a lower number of days at V4. No adverse events were reported.

Conclusion. Treatment of LBP and sciatica is a major concern. Although the natural history of acute LBP is often self-limiting, conservative therapies are not always effective; in such cases, O₂O₃ intramuscular lumbar paravertebral injections, which are minimally invasive, seem to safely and effectively relieve pain, as well as reduce both disability and the intake of analgesic drugs.

Key words: acute low-back-pain, radiating pain, lumbar disc herniation, oxygen-ozone therapy. Spine 2009; 34:1337–1344

Acute low back pain (LBP) is a major cause of disability, including impairment in daily living activities and socioeconomic problems. Acute LBP is defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs that is of less than 6 weeks’ duration. Radicular pain is defined as a pain that radiates below the knee whereas pseudoradicular pain does not go beyond the knee. Although the exact pathogenesis of acute LPB remains unclear, the prevalence of lumbar disc herniation (LDH) is estimated to be higher in patients with acute LBP than that in asymptomatic people (57% and 20%–28%, respectively). Although internal disc disruption remains a controversial issue, it has been suggested that this condition is a major cause of acute LBP. Indeed, internal disc disruption has been reported to be a cause in about 73% of cases of acute LBP and, when associated with LDH, as a cause in about 40% cases of radiating pain. Although the natural history of LDH tends to be favorable, relapses and recurrences are common, and low levels of pain and disability may persist in some patients.

Numerous therapeutic interventions for the treatment of LDH have been studied and performed, including noninvasive treatments, minimally invasive procedures, and surgery. It was recently demonstrated that back pain improved in intervertebral disc herniation patients treated both surgically and nonsurgically, though the degree of improvement was significantly greater in patients who underwent surgery; the difference between patients who underwent surgery and those who did not remain statistically significant at 2 years. Relief from leg
pain was also greater in the surgically-treated group, and the degree of relief was greater than that reported for LBP. 16

Minimally invasive treatments, such as percutaneous injections, a well-tolerated, low-cost procedure, have been shown to yield good clinical results, 17 though no single treatment has yet proved to be clearly superior to any other. 18–20

Recent findings 17,21–23 have shown that oxygen-ozone (O2O3) therapy can be used to treat LDH that fails to respond to conservative management, either before recourse to surgery or when surgery is not possible.

O2O3 therapy is used in medicine to treat various conditions 24,25 and is based on the exploitation of the chemical properties of oxygen (O3), an unstable allotropic form of oxygen. In the treatment of LDH, O2O3 therapy has been proposed above all because it has: (i) a direct effect on the proteoglycans composing the disc’s nucleus pulposus, which results in the release of water molecules and the subsequent cell degeneration of the matrix; this matrix is in turn replaced by fibrous tissue, which leads to a reduced disc volume 23; (ii) analgesic and anti-inflammatory effects, which may counteract disc-induced pain. 17,25 As reported by Bonetti et al.,22 a CT-guided intraforaminal infiltration of an O2O3 gas mixture seems to be as effective as periradicular steroid infiltrations in patients affected by chronic and acute LBP at the 1-week follow-up, while at the 6-month follow-up results are even better in patients with disc disease who receive O2O3 therapy than in those who receive steroid infiltrations. 22 Moreover, intraforaminal and intradiscal injections of a combination of O2O3, steroids, and an anesthetic are more effective at 6 months than injections of a steroid and an anesthetic alone in the same sites in the management of radicular pain related to acute LDH. 23 According to Andreula et al.,17 a combined intradiscal and periganglionic injection of medical O3 and a periganglionic injection of steroids has a cumulative effect that enhances the overall outcome of treatment for pain caused by disc herniation. 17

However, these findings are based on intradiscal/ intraforaminal O2O3 injection, whereas intramuscular-paravertebral injection is the technique used most in clinical practice in Italy and other Western countries. For this reason, the Italian Public Health Ministry has recently encouraged scientific institution to promote clinical trials in this field. Otherwise on November 2006, the Istituto Superiore di Sanità, the leading technical and scientific public body of the Italian National Health Service, has promoted a Consensus Conference about lumbar paravertebral intramuscular injection of O2O3 in radicular pain caused by LDH, which results have been recently published.26

To assess the short- and long-term impact of intramuscular-paravertebral O2O3 injection on acute LBP, we conducted a multicenter, randomized, double-blind, “simulated therapy”-controlled clinical trial in a cohort of patients with LDH. The aim of our trial was to assess the benefit, if any, of O2O3 therapy as opposed to simulated injection in this target group, as expressed in terms of the number of pain-free patients at the end of treatment and treatment continuation.

Materials and Methods

Patients of both sexes aged between 18 and 65 years, seen between October 2004 and December 2006 in 3 medical rehabilitation centers in the North (Studio Medico Prof. Franzini, Bergamo, Italy), South (CMR spa, Centro Medico di Diagnostica e Riabilitazione, Sant’Agata di Goti [BN]), and center of Italy (Physical Medicine and Rehabilitation Unit, Azienda Polyclinico Umberto I, Roma), were included if they reported acute LBP and/or radiating pain of moderate to severe intensity (≥5 on a 10-cm visual analog scale [VAS]) to one leg, and MRI evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months. Radiating pain was defined as pain, of less than 10 days’ duration in a patient who has been pain-free in the previous 3 months, that radiates down the posterior or lateral part of the leg beyond the knee, with positive findings (reproduction of symptoms) at nerve tension tests (i.e., straight leg raise or bowstring).

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.

Disc abnormalities were classified according to the Modic classification 27 and subjects with 4A herniated disc (protrusion with an intact anulus) were included in the study.

Exclusion criteria were: clinical signs of radiculopathy (i.e., tendon reflex loss, myotomal weakness, sensory abnormalities); cauda equina syndrome, progressive neurologic deficit, and/or steppage due to complete L4–L5 damage, considered as evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months.

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.

Disc abnormalities were classified according to the Modic classification 27 and subjects with 4A herniated disc (protrusion with an intact anulus) were included in the study.

Exclusion criteria were: clinical signs of radiculopathy (i.e., tendon reflex loss, myotomal weakness, sensory abnormalities); cauda equina syndrome, progressive neurologic deficit, and/or steppage due to complete L4–L5 damage, considered as evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months. Radiating pain was defined as pain, of less than 10 days’ duration in a patient who has been pain-free in the previous 3 months, that radiates down the posterior or lateral part of the leg beyond the knee, with positive findings (reproduction of symptoms) at nerve tension tests (i.e., straight leg raise or bowstring).

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.

Disc abnormalities were classified according to the Modic classification 27 and subjects with 4A herniated disc (protrusion with an intact anulus) were included in the study.

Exclusion criteria were: clinical signs of radiculopathy (i.e., tendon reflex loss, myotomal weakness, sensory abnormalities); cauda equina syndrome, progressive neurologic deficit, and/or steppage due to complete L4–L5 damage, considered as evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months.

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.

Disc abnormalities were classified according to the Modic classification 27 and subjects with 4A herniated disc (protrusion with an intact anulus) were included in the study.

Exclusion criteria were: clinical signs of radiculopathy (i.e., tendon reflex loss, myotomal weakness, sensory abnormalities); cauda equina syndrome, progressive neurologic deficit, and/or steppage due to complete L4–L5 damage, considered as evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months. Radiating pain was defined as pain, of less than 10 days’ duration in a patient who has been pain-free in the previous 3 months, that radiates down the posterior or lateral part of the leg beyond the knee, with positive findings (reproduction of symptoms) at nerve tension tests (i.e., straight leg raise or bowstring).

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.

Disc abnormalities were classified according to the Modic classification 27 and subjects with 4A herniated disc (protrusion with an intact anulus) were included in the study.

Exclusion criteria were: clinical signs of radiculopathy (i.e., tendon reflex loss, myotomal weakness, sensory abnormalities); cauda equina syndrome, progressive neurologic deficit, and/or steppage due to complete L4–L5 damage, considered as evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain. Acute LBP was defined as pain that occurs posteriorly in the region between the lower rib margin and the proximal thighs for less than 10 days in a patient who has been pain-free in the previous 3 months. Radiating pain was defined as pain, of less than 10 days’ duration in a patient who has been pain-free in the previous 3 months, that radiates down the posterior or lateral part of the leg beyond the knee, with positive findings (reproduction of symptoms) at nerve tension tests (i.e., straight leg raise or bowstring).

Local and radiating pain were assessed using a 10-cm horizontal VAS with 0 cm labeled “no pain” and 10 cm “worst pain I have ever had.” Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or radiating pain in the last week?” by placing a mark somewhere along the line.
tients who were pain-free at the end of treatment (pain-free patients, were blind to the assigned treatments. The assessors who were different from the investigators who enrolled the participants were read by the same radiologist in each center and disc protrusion changes were assessed using the Modic criteria.  

Patients in the SG received 15 intramuscular infiltrations (3/wk for 5 consecutive weeks) of an O₃₂O₃ mixture (20 mL) with an O₃ concentration of 20 µg/mL, obtained by means of a Multiossigen PM95 generator (Multiossigen s.r.l., Gorle, Bergamo, Italy). The intramuscular injection was administered in the paraspinous lumbar muscles, bilaterally (10 mL for each side) using an extraspinal lateral approach, under sterile conditions, using a 22-gauge needle. The sites most frequently treated were those corresponding to L₄–L₅ (65%) and L₅–S₁ (25%). An injection time of 15 seconds was used, since a longer injection time was deemed unsuitable because of the instability of medical O₃, which starts decaying (2 µg/mL) after about 20 seconds. No premedication or anesthesia was given, and the procedure was performed in an outpatient clinic.  

Patients in the CG received simulated treatment that lasted as long as the O₃₂O₃ treatment (15 infiltrations, 3/wk for 5 consecutive weeks). The simulated injection was administered using a false needle that pricked the skin without piercing it, applied at the lumbar paraspinous level, followed by hand-applied pressure on the same site designed to reproduce the load sensation commonly described after O₂O₃ injections.  

To avoid possible blinding failure, the injection site in patients in both groups was covered with a water-proof plaster that was removed by the treating physician before the subsequent treatment session.  

Both the active and simulated treatments were administered by the same physician at each center, who had received formal training in O₂O₃ therapy. After admission, the patients received an ad hoc diary in which they were asked to record, throughout the observation period, the days of pain, any non-steroidal anti-inflammatory drugs prescriptions, including the dose and kind of prescription. No opiates, steroids, or physical methods (e.g., therapeutic exercise, traction, physical therapy) were allowed. Daily variations in pain were assessed by means of a 10-cm horizontal VAS with 0 cm labeled no pain and 10 cm worst pain I have ever had. Subjects were asked to answer the question: “referring to the worst pain you have experienced in your life, what was the relative level of your back pain or sciatica today?” and responded by placing a mark somewhere along the line. Patients were also assessed for pain (VAS) and for disability related to the LBP (Backill questionnaire) at the scheduled visits during the treatment period (15 V2 and 30 V3 days after treatment started) and after treatment ended (2 weeks V4, and 3 V5 and 6 V6 months). The assessors who were different from the investigators who enrolled the participants, were blind to the assigned treatments.  

The primary outcome measures were: (i) the number of patients who were pain-free at the end of treatment (pain-free condition was defined as a VAS score ≤1) and (ii) treatment failure, which was defined by the number of patients who interrupted the treatment they had been assigned because of no benefit (no reduction in pain). Participants were free to interrupt or continue the assigned treatment depending on their impressions of improvement and satisfaction.  

Secondary outcome measures included changes in the Backill questionnaire score at each follow-up, changes in the VAS score at each follow-up, the mean number of days on non-steroidal anti-inflammatory drugs during the treatment period, and the number of cases in which MRI (at 45 days) revealed at least a reduction in disc protrusion.

### Statistical Analysis

Statistical analysis was performed using the SSP 2.5 statistical package (Smith’s Statistical Package, version 2.75, 2004, Gary Smith, Pomona College, Claremont, CA). All primary and secondary outcome analyses were performed according to the principle of intention-to-treat. The intention-to-treat analysis was carried out according to a “worst-case-scenario” analysis: subjects who did not complete the treatment or had not undergone the posttreatment or final follow-up assessments were assigned a poor outcome, corresponding to the final average change recorded in the protocol completer population in the CG. The χ² or Fisher exact test, Student t test or the Mann-Whitney U test, and analysis of variance (ANOVA) were used, as appropriate. The choice of parametric or nonparametric tests was dictated by the results of a normality test. A 2-way ANOVA with group (treatment vs. control) as the between-subjects factor and time as the within-subjects factor was used to assess the presence of significant differences between the SG and CG and within each group before and after treatment and at the 6-month follow-up. A Tukey post hoc comparison was used to identify significant differences between mean values when a significant main effect and interaction were found. For all analyses, the level of significance was set at P < 0.01.

Sample size was calculated under the assumption that 20% of patients randomized to simulated therapy and 55% of those randomized to O₂O₃ would be pain-free at the end of the treatment. On this basis, the minimum number of patients to be enrolled in each treatment arm would be 23 with at least 80% of power and 5% significance.

### Results

During the study period, 327 outpatients with at least moderate acute LBP were seen at the study centers. Of these, 267 were not randomized because they were either ineligible (n = 225) or because they declined the invitation to participate (n = 42) (Figure 1). A total of 60 patients were randomized to either the SG (n = 36) or CG (n = 24). Table 1 summarizes the patients’ main clinical features. The 2 treatment groups were fairly well-balanced as regards pain intensity.  

At the end of follow-up, there was a significant difference between the SG and CG in the percentage of cases who had become pain-free (61% vs. 33%, P < 0.01) (Table 2).

Six patients (SG: 2 [5.6%]; CG: 4 [16.7%]) interrupted the treatment before the end of the study period because of unsatisfactory results (Figure 1).
Patients who received O₂O₃ had a lower mean VAS score at V2 than the patients who received simulated therapy (mean difference 1.5) (Figure 2). The mean difference increased slightly at the subsequent visits, the peak (2.3) being reached at V6. These differences were significant at the 2-way ANOVA (F: 43,390; \( P < 0.0001 \)).

A significant improvement was observed in the Backill scores in the SG patients, when compared with the CG patients, at V3, V4, V5, and V6 (mean difference 3.6, 7.6, 10.3, and 8.9, respectively) (Figure 3). An improvement was observed in the Backill scores between the baseline and final follow-up in both groups (SG: +13.0; CG: +5.6), but reached significance in the SG alone.

Active O₂O₃ therapy was followed by a significantly lower number of days on nonsteroidal anti-inflammatory drugs at V2 and V3 and by a lower (though not significant) number of days at V4. No drug intake was reported at V5 and V6 (Table 2).

There were no statistically significant differences in the Kellner symptom scores and SF-36 scores between groups (Table 3). Follow-up MRI findings were unchanged from baseline for all the patients in both groups. No adverse events were reported.

### Table 1. Patient’s Main Clinical Features

<table>
<thead>
<tr>
<th>Variable</th>
<th>Study Group</th>
<th>Control Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>Total</td>
<td>36</td>
<td>100</td>
</tr>
<tr>
<td>Sex</td>
<td>18</td>
<td>50</td>
</tr>
<tr>
<td>Male</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Lumbar</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Radiating pain–left leg</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Radiating pain–right leg</td>
<td>12</td>
<td>33.3</td>
</tr>
<tr>
<td>Mean (yr)</td>
<td>48.8</td>
<td>13.6</td>
</tr>
<tr>
<td>VAS*</td>
<td>7.14</td>
<td>0.66</td>
</tr>
<tr>
<td>Backill†</td>
<td>26</td>
<td>5.1</td>
</tr>
</tbody>
</table>

*VAS at baseline (V1).
†Backill questionnaire score at baseline (V1).
Discussion

The results of our study show that paravertebral intra-
muscular O₂O₃ injections, when compared with simu-
lated therapy, afford greater pain relief, as demonstrated
by higher number of pain-free subjects at the final fol-
low-up examination in the SG, and reduce drug intake in
people affected by acute LBP and/or radiating pain
caused by LDH. This reduction in pain is reflected not
only in a significant improvement in the Backill question-
naire score, which points to a reduced perception of LBP-
related disability, but also in the significantly lower pa-
tient drop-out rate because of persisting pain during the
treatment period.

These observations are not, however, accompanied by
MRI changes in disc abnormalities. It should, neverthe-
less, be pointed out that the pathophysiology of LBP and
radicular pain has not yet been fully understood. Indeed,
the mechanical effect of nerve root compression
does not seem to completely explain radicular pain. In-
flammatory changes have been observed in lumbar disc
and periradicular tissues in people suffering from lumbar
and radiating pain, and a correlation has been found be-
 tween inflammatory changes in herniated lumbar disc speci-
men and outcome after lumbar disc surgery, with a lower VAS rating in those patients showing inflammatory changes in the herniated disc after surgery.

Both chronic compression and the antigenic proper-
ties of the nucleus polposus are presumable causes of the
inflammatory reaction. Given the inclusion criteria
adopted in our study, in which only subjects with a
Modic stage 27 of herniated disc (protrusion with an
intact anulus) were considered, we may assume that the
inflammatory pain in our patients was due mostly to
chronic mechanical compression, rather than to an im-
mune reaction against the nucleus polposus. Conse-
quently, the possible mechanism of action of the O₂O₃
mixture may be found in the biochemical properties of
O₃. Indeed, numerous biologic effects have been attrib-
ted to this unstable allotropic form of oxygen, including
an immunomodulating action and analgesic and anti-
flammatory effects. This action is correlated with:
(i) the inhibited synthesis of proinflammatory
prostaglandins, the release of bradykinin, or the release
of algogenic compounds; (ii) the increased release of an-
tagons or soluble receptors that neutralize proinflam-
matory cytokines, such as interleukin (IL)-1, IL-2, IL-8,
IL-12, IL-15, interferon-α, and tumor necrosis factor-α
(TNF-α); (iii) the increased release of immunosuppressor
cytokines, such as transforming growth factor-β1 and
IL-10.
In our patients, an O₃ concentration of 20 μg/mL was used to avoid the risk of toxicity. Indeed, O₃ concentrations >60 μg/mL potentially exceed the capacity of antioxidant enzymes (superoxide dismutase and catalase) and glutathione to prevent accumulation of the superoxide anion (O₂⁻) and hydrogen peroxide (H₂O₂), which can cause cell membrane degradation.⁴²

No adverse events were observed in our series in either the SG or CG. A case of fatal septic shock after intramuscular-paravertebral O₃ injection was recently reported in one study.⁴³ The authors of that study suggested that acute fatal septicemia should be considered as one of the possible major complications of O₂O₃ therapy in the treatment of a LDH. However, secondary septicemia after an invasive maneuver should be considered as a complication due to an inadequate asepsis procedure. Because we administered the therapy using a sterile procedure, every precaution was taken to avoid the risk of infection at the injection site.

Our results are only slightly inferior to those presented by Bonetti et al.,²² who found, after studying 306 patients randomly treated with either a CT-guided intraradicular injection of O₂O₃ or periradicular steroid injections, that 84% and 74% of patients treated with O₂O₃ were pain-free respectively at the 1-week and 6-month follow-ups. However, since those authors included patients with both chronic and acute LBP, our results may only be partly comparable. Moreover, no mention was made by those authors of disability caused by LBP, which, in our experience, strongly influences the clinical outcome.

At the 6-month follow-up, our results seem to be comparable, in terms of pain reduction, disability, and drug consumption, to those obtained by means of a combined intradiscal and periganglionic injection of medical O₃ and a periganglionic injection of steroids.¹⁷ Some concern still surrounds exactly how the gas mixture is distributed after the injection. As we did not perform a pre/post MRI control, we could not study whether the O₂O₃ mixture reached the periradicular space. However, since the MRI findings were not modified at the 45-day follow-up, one may speculate that the action of O₂O₃ is exerted above all on the molecular inflammatory aspects of LBP and radicular pain, and not mechanically on root compression by the protruded lumbar disc. Indeed, as demonstrated by Igarashi et al.,¹⁴ facet joint tissues of patients with LDH display an increased level of inflammatory cytokines, though it remains lower than that of patients with lumbar degenerative disor-

---

<table>
<thead>
<tr>
<th>SF-36 health survey</th>
<th>Study Group</th>
<th>Mean</th>
<th>SD</th>
<th>Control Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical functioning</td>
<td>65.2</td>
<td>13.9</td>
<td>62.1</td>
<td>21.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role, physical</td>
<td>29.1</td>
<td>35.4</td>
<td>29.3</td>
<td>35.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bodily pain</td>
<td>31.8</td>
<td>10.3</td>
<td>31.8</td>
<td>12.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General health</td>
<td>56.4</td>
<td>17.0</td>
<td>57.6</td>
<td>18.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitality</td>
<td>55.7</td>
<td>14.1</td>
<td>54.4</td>
<td>15.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Social functioning</td>
<td>56.2</td>
<td>12.7</td>
<td>54.0</td>
<td>14.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Role, emotional</td>
<td>45.1</td>
<td>42.8</td>
<td>42.8</td>
<td>39.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health</td>
<td>73.5</td>
<td>13.9</td>
<td>70.2</td>
<td>11.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Kellner rating scale</th>
<th>Study Group</th>
<th>Mean</th>
<th>SD</th>
<th>Control Group</th>
<th>Mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anxiety</td>
<td>6.2</td>
<td>2.6</td>
<td>6.0</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety symptoms</td>
<td>3.3</td>
<td>2.3</td>
<td>3.5</td>
<td>1.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relaxed</td>
<td>2.4</td>
<td>1.6</td>
<td>2.5</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>4.0</td>
<td>3.1</td>
<td>4.0</td>
<td>2.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression symptoms</td>
<td>2.0</td>
<td>1.9</td>
<td>2.2</td>
<td>1.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Contented</td>
<td>2.1</td>
<td>1.7</td>
<td>2.2</td>
<td>1.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic</td>
<td>9.1</td>
<td>3.8</td>
<td>8.9</td>
<td>4.1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic symptoms</td>
<td>5.3</td>
<td>3.2</td>
<td>5.3</td>
<td>4.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somatic well-being</td>
<td>4.4</td>
<td>1.7</td>
<td>4.3</td>
<td>1.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger-hostility</td>
<td>3.5</td>
<td>2.9</td>
<td>3.3</td>
<td>2.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anger-hostility</td>
<td>2.1</td>
<td>2.5</td>
<td>2.2</td>
<td>2.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Friendly</td>
<td>1.1</td>
<td>1.1</td>
<td>1.2</td>
<td>1.3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It could thus be speculated that inflammation of facet joints accounts for part of the pain in lumbar disorders, even when associated with LDH. From this point of view, the $O_2O_3$ injection at a paraspinal level may act as local antiphlogistic therapy.

One study recently demonstrated that nerve root compression may lead to morphologic changes in the dorsal horn of the lumbar cord. The authors of that study speculate that nerve root compression disrupts the axonal flow in the nerve fibers of the dorsal root, which in turn causes Wallerian degeneration. Assuming that this is true, the $O_2O_3$ mixture may even exert its effects far from its application site on account of its antiphlogistic properties, which would improve axonal function. In particular, since TNF-$\alpha$ seems to play a key role in inducting apoptosis of dorsal root ganglion cells, the antagonistic effect exerted by the $O_2O_3$ mixture on TNF-$\alpha$ may play an important protective role.

Another possible explanation for the therapeutic effect of injections may be a direct effect of the injection procedure on trigger points in the paraspinal musculature. Indeed, dry needling of trigger points has been shown to relieve pain in patients with myofascial pain syndrome, even if to a lesser degree than a lidocaine injection. However, since myofascial pain syndrome patients more typically present neck pain or shoulder girdle pain, as opposed to LBP, we believe that trigger points are less likely to have had such an effect on acute LBP in our sample. Consequently, the therapeutic effect we observed is more likely to be due to the properties of the $O_2O_3$ mixture than to the needling itself.

The main limitation of this study is the possible failure of the blinding procedure. Because we did not conduct an exit interview designed to investigate the patients’ perceptions of the therapy they had received, we cannot exclude the occurrence of unmasking. However, we attempted to reduce the possibility of blinding failure by excluding patients who had previously received $O_2O_3$ infiltrations and by masking the injection site.

As the external validity of our results is limited by the fact that only LBP with disc protrusion was considered, the findings need to be verified by replicating the study in other settings. Moreover, only patients who had been pain-free in the previous 3 months were included in our study; this means that we may have included some patients affected by recurrent LBP, i.e., recurring episodes of acute LBP with pain-free intervals of more than 3 months. It should be borne in mind that this may have biased our results because of the differences in the natural history of these conditions. However, the fact that the natural history of a first episode of acute LBP is generally more favorable than that of recurrent LBP might have resulted in a worsening effect on the clinical outcomes of our patients.

The action of the $O_2O_3$ mixture may be reduced by the rapid decay to which it can be subject. However, we believe that this drawback can be avoided by injecting the gas shortly after it is produced, as specified in our protocol.

Lastly, as no cost-effectiveness analysis was performed in our study, no conclusions can be drawn in this regard; it should, however, be pointed out that this minimally invasive procedure can be performed, as it was in this study, in an outpatient clinic without any radiologic armamentarium, and is thus a relatively inexpensive form of therapy.

**Conclusion**

Treatment of acute LBP with or without radiating pain is a major concern. Although the natural history of acute LBP is often self-limiting, conservative therapies are not always effective; in such cases, $O_2O_3$ intramuscular lumbar paravertebral injections, which are minimally invasive, seem to safely and effectively relieve pain, as well as reduce both disability and the intake of analgesic drugs.

**References**