Intraforaminal O_2-O_3 versus Periradicular Steroidal Infiltrations in Lower Back Pain: Randomized Controlled Study

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BACKGROUND AND PURPOSE: **Reports about steroids and oxygen-ozone therapy to treat lower back pain have been increasing. The purpose of our study was to compare the clinical outcomes in patients treated with infiltrations of O_2-O_3 gas or steroids at short-, medium-, and long-term follow-up.**

METHODS: **A total of 306 patients (166 with primarily disk disease, 140 with nondisk vertebral disease) with acute or chronic low back and sciatic nerve pain received a CT-guided intraforaminal infiltration of an O_2-O_3 gas mixture or an periradicular infiltration of steroids. Neurologists unaware of the type of treatment assessed the patients.**

RESULTS: **At 1-week follow-up, most patients had a complete remission of pain, regardless of the treatment. At 6-month follow-up, differences in favor of O_2-O_3 treatment were significant in patients with disk disease ($P = .0021$) but not in those without disk disease ($P = .0992$). Clinical outcomes were poor in 13 (15.1%) of 86 patients receiving O_2-O_3 infiltration and in 18 (22.5%) of 80 patients receiving steroid injection ($P = .2226$). Among patients without disk disease, six (8.6%) of 70 patients receiving O_2-O_3 infiltration but 21.4% of the patients receiving steroid injections had poor outcomes ($P = .0332$).**

CONCLUSION: **Oxygen-ozone treatment was highly effective in relieving acute and chronic lower back pain and sciatica. The gas mixture can be administered as a first treatment to replace epidural steroids.**

Lower back pain with or without sciatic nerve involvement affects roughly 80% of the population at least once in their lifetime. In addition, lower back pain is the leading cause of lost working days, which has a major effect on national healthcare spending (1). Until 15 years ago, surgery was the treatment of choice, but conservative measures are now preferred in the wake of unsatisfactory surgical outcomes (2). Among the techniques adopted in the past decade to treat sciatic nerve pain caused by a herniated disk or nondiskal spinal disease (osteophytosis, spondylolysis, facet joint syndrome, etc.) are the periradicular infiltration of a steroid and the intraforaminal injection of an O_2-O_3 gas mixture. Both methods have yielded encouraging results (3–7).

We compared the therapeutic effectiveness of these methods, undertaking a randomized controlled study in 306 patients with acute or chronic low back pain and sciatica. Patients were treated with either an intraforaminal infiltration of an O_2-O_3 gas mixture or the periradicular infiltration of steroid.

Methods

Between March 2001 and December 2003, 306 patients (178 men, 128 women; age range, 26–72 years; mean age, 48 years) with acute or chronic low back and sciatic nerve pain were treated. All patients provided informed consent. Patients received CT-guided infiltration of an O_2-O_3 gas mixture or a steroid, and they were told that both were effective treatments according to recent findings reported in medical literature.

On their enrollment, the name, date of birth, date of enrollment, date of treatment and clinical details were recorded for each patient. We recorded the type of pain, irradiation, paresthesias, presence of the Lasègue sign, degree of sensitivity, lower limb reflexes, plantar extension of the foot, and dorsal extension of the big toe. Their records also included details about the type of treatment given (steroid or O_2-O_3 mixture), but this information was withheld from the neurologists performing the follow-up assessment. Patients had acute or

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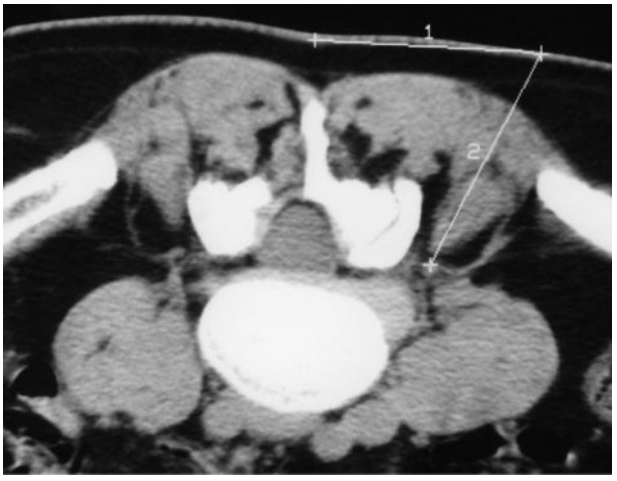

FIG 1. Preliminary CT measurements, periganglionic approach.

chronic low back pain and sciatica, which was unilateral or which radiated along the innervation territories of L3 (18 patients), L4 (89 patients), L5 (135 patients), or S1 (64 patients). The duration of their symptoms was 1–20 months. Six patients had previously received an epidural infiltration of steroids without a notable improvement in symptoms.

Patients with bilateral lower back and sciatic nerve pain and those with electromyographic features of neurogenic injury and/or denervation were excluded and advised to seek neurosurgical treatment.

Before their enrollment, all patients had undergone CT or MR imaging. On the basis of depicted neuroradiologic changes, patients were divided into two groups: the disk-disease group, or those with mainly disk disease (e.g., bulging disk, protrusion or extrusion; $n = 166$), and the non–disk-disease group, or those with nondisk vertebral disease (e.g., osteophytosis, spondylolysis, facet joints syndromes; $n = 140$). Of the 166 patients with disk disease, 80 were treated by means of steroid injection, whereas the remaining 86 received an infiltration of an O_2-O_3 gas mixture. Of the140 patients without disk disease, 70 received steroid injections, and 70 were received infiltrations of the O_2-O_3 gas mixture.

In all patients, the injection site was disinfected, and local anesthesia applied by using an ethyl chloride spray. Infiltrations were done by specialist neuroradiologists at our institutions. The puncture site was identified on CT scans and marked on the patient's skin. The distance from this point to the foramen was subsequently measured (Fig 1).

A 22-gauge needle (Terumo, Leuven-Belgium) was positioned 2–3 mm from the foraminal region, close to the ganglion of the affected nerve root. A 9-cm needle was typically used, but longer needles were occasionally needed depending on the size of the patient. CT scanning was performed to check correct needle placement. This procedure was used for infiltrations of both the O_2-O_3 mixture and the steroid (Figs 2–4).

Infiltrations of steroid 2 mL (80 mg, Methylprednisolone acetate; Depomedrol, Pfizer, Italy) was completed without contrast medium, by paying special attention to the speed of infiltration. The procedure was completed slowly (over 1–2 minutes) to avoid the reflux of steroid along the needle trajectory. Patients with facet joint syndrome received injections into the surrounding joint capsule.

O_2-O_3 was infiltrated by injecting 3 mL of the gas mixture at a rate of 25 μg/mL close to the neural foramen. The needle was then retracted a few millimeters and another 5 mL of the mixture was injected to involve the facet joint region. CT scans were used to check the correct distribution of the gas mixture in the foramen and facet joint. All treatments were performed by using equipment allowing the photometric detection of the concentration of O_3 in the gas mixture (i.e., the device automatically corrected the change in concentration that occurred when the syringe was withdrawn), with constant pressure during the O_3-intake operation. We observed no toxicity effects as the titanium, Teflon, glass, and silicon, which are inert to the O_3, were in contact with the gas (CE mark class 1B Alnitec device [Alnitec Cremosano, Italy]).

Teams of neuroradiologists (M.B., A.F., B.C.) from two hospitals performed the infiltrations in both groups of patients, and two neurologists (G.D.V., M.G.) blinded to the type of treatment performed the clinical follow-up. The neurologists assessed the short (1-week), medium (3-month) and long-term (6-month) outcomes of treatment by using a modified version of the McNab method. Outcomes were classified as excellent, which was the resolution of pain and return to activity before the onset of pain; good or satisfactory, which was a reduction of pain by 50% or more; or mediocre or poor, which was partial reduction of pain by 30% or less.

For statistical analysis, the χ^2 test was used.

Results

The Table summarizes the patients' outcomes. At short-term follow-up after treatment with steroid or O_2-O_3, patients with disk disease (80% or 84.8%, respectively) and those without disk disease (78.5% or 80%, respectively) had a complete remission of pain. Therefore, good outcome were observed regardless of the treatment, although the difference was not statistically significant ($P = .4077$). At medium-term follow-up, 77.9% of the patients with disk disease and 78.5% of those without disk disease were pain free after O_2-O_3 infiltration, compared with 67.5% and 70%, respectively, of those treated with steroid ($P = .1318$ and .2460, respectively).

At long-term follow-up, 46 (57.5%) of 80 patients in the disk-disease group who were treated with Depomedrol deemed the clinical outcome to be excellent, as did 44 (62.8%) of 70 patients in the non–disk-disease group after steroid infiltration. After O_2-O_3 infiltration, 64 (74.4%) of 86 patients with disk disease reported complete remission of pain, as did 53 (75.8%) of 70 patients without disk disease. Differences in favor of O_2-O_3 treatment were significant in patients with disk disease ($P = .0021$) but not in those without disk disease ($P = .0992$).

In the disk-disease group, 13 (15.1%) of 86 patients treated with O_2-O_3 infiltration, and 18 (22.5%) of 80 patients treated with steroid injection deemed their clinical outcome poor ($P = .2226$). Among patients without disk disease, six (8.6%) of 70 patients receiving O_2-O_3 infiltration but 21.4% of the patients receiving steroid injections had poor outcomes ($P = .0332$).

Discussion

Our short-term outcomes were similar in both groups of patients, irrespective of the type of infiltration administered. The basis of this pain relief with steroid or O_2-O_3 infiltration appears to reflect be the origin of nerve root pain. Zennaro et al (8) reported that low back pain and sciatica have a neuritic origin, which reduces the role of disk herniation as the sole factor responsible for pain. In fact, episodes of back

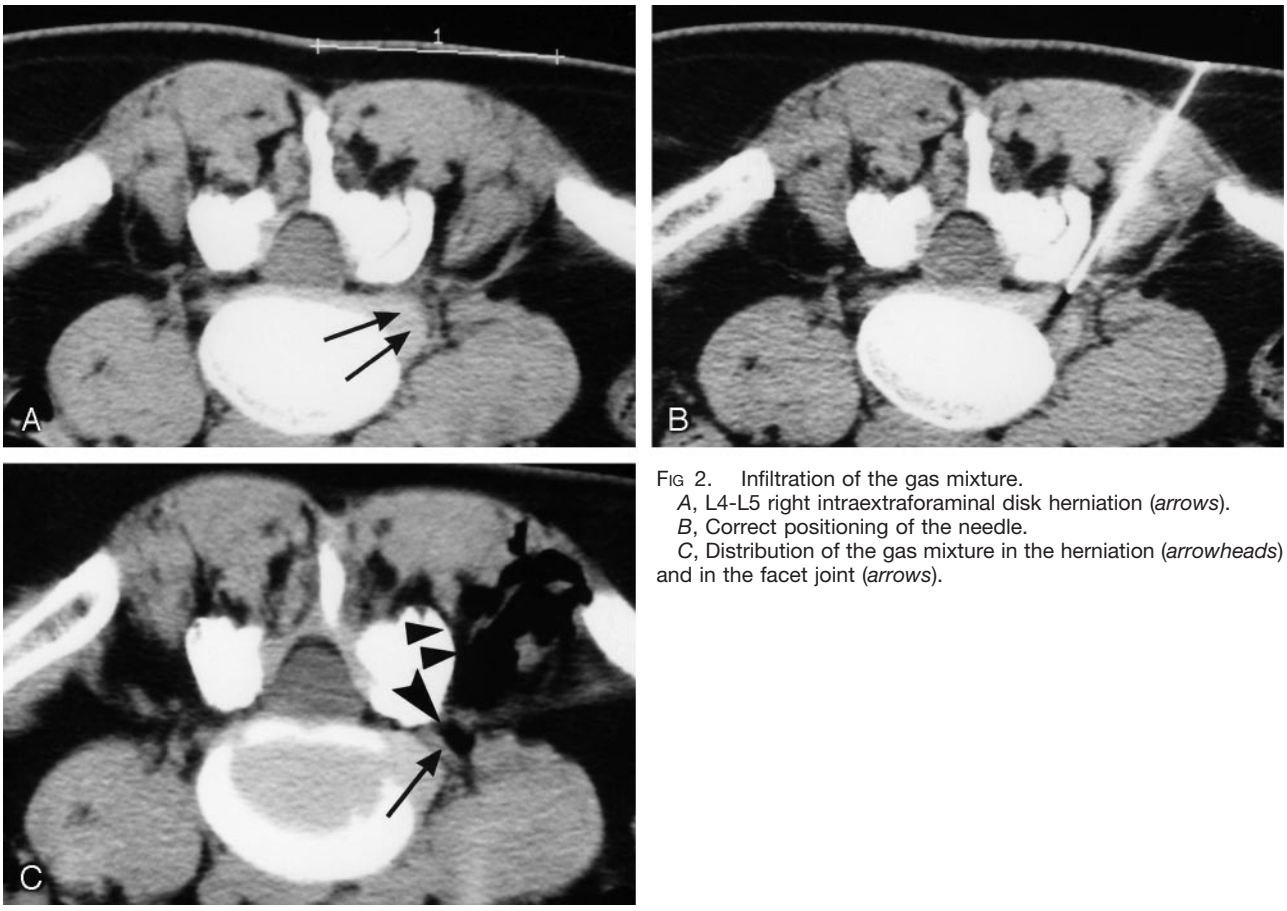

FIG 2. Infiltration of the gas mixture.
A, L4-L5 right intraextraforaminal disk herniation (*arrows*).
B, Correct positioning of the needle.
C, Distribution of the gas mixture in the herniation (*arrowheads*) and in the facet joint (*arrows*).

pain and sciatica are linked to factors not strictly connected to the mechanical compression of the nerve root, but rather, they caused by an nonspecific inflammatory reaction to the autoantigens of the mucopolysaccharide matrix located on the disk surface and exposed to the immune system by migration of the disk nucleus beyond the natural barrier of the annulus fibrosus (2, 9). The inflammatory reaction is linked to release of lytic enzymes, such as E2 prostaglandins and A2 phospholipase. These enzymes are present in the peridiskal epidural adipose environment in quantities a hundred-fold higher in patients with disk herniation than in those with a bulging disk alone, confirming the postulated inflammatory origin of their pain (10–13).

In addition, larger amounts of herniated disk material is known to be linked to faster degeneration of the disk fragment, probably resulting from enhanced macrophage activity triggered by the strong inflammatory reaction (14). The resulting inflammation affects the root ganglion, namely, its nociceptive C fibers, increasing their mechanical sensitivity and giving rise to a painful stimulus. This effect also occurs by means of ephaptic transmission (i.e., functional contact among neuron fibers in which impulses jump to a contiguous inactive fiber not at the synapse but across the membrane) in the apparent absence of mechanical compression (15).

The rationale for anti-inflammatory treatment with

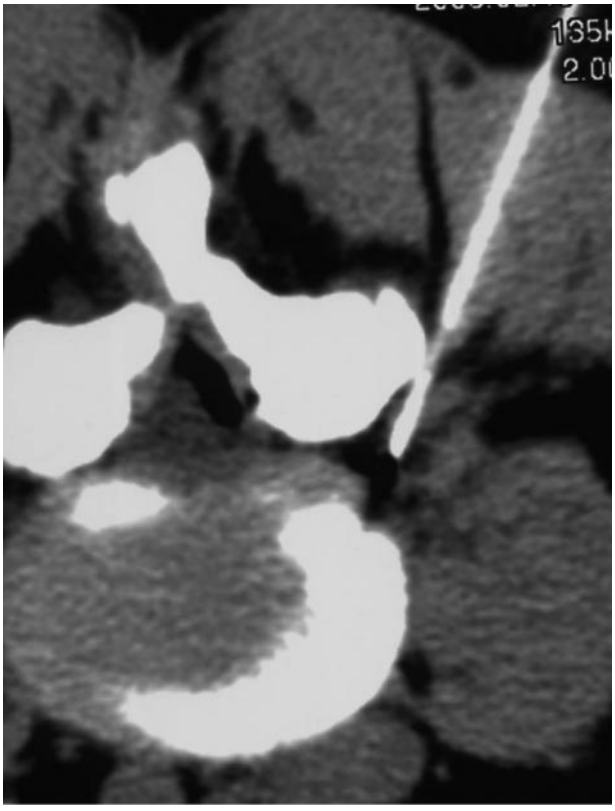

FIG 3. After intraforaminal infiltration, the gas mixture is distributed between the posterior longitudinal ligament and the dural sheath.

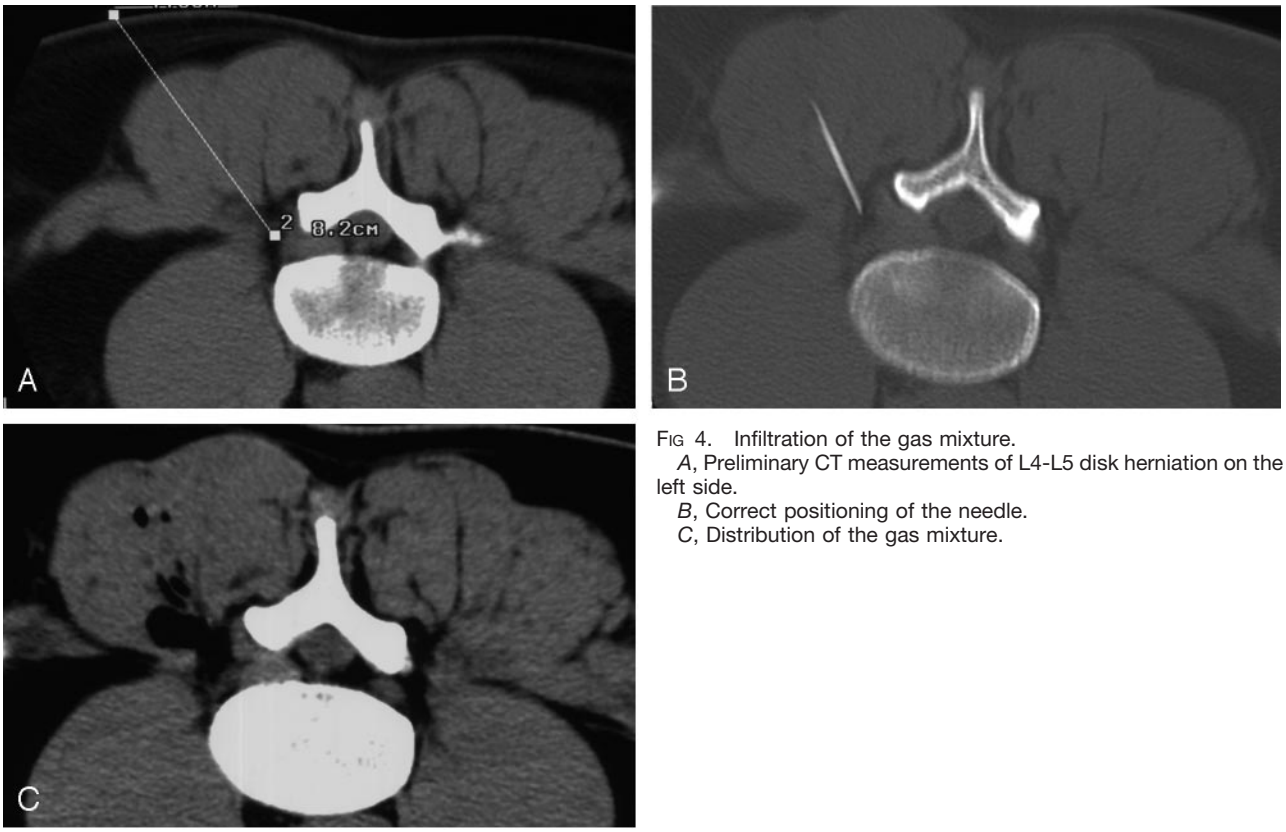

FIG 4. Infiltration of the gas mixture.
A, Preliminary CT measurements of L4-L5 disk herniation on the left side.
B, Correct positioning of the needle.
C, Distribution of the gas mixture.

Results from short-, medium- and long-term follow-up

Follow-Up and Patients	Outcome with O_2-O_3			Outcome with Steroid		
	Excellent	Good	Poor	Excellent	Good	Poor
Short term						
With disk disease (n = 166)	73 (84.8%)	8 (9.3%)	5 (5.9%)	64 (80%)	10 (12.5%)	8 (10%)
Without disk disease (n = 160)	56 (80%)	11 (15.7%)	3 (4.3%)	55 (78.5%)	9 (12.8%)	5 (7.2%)
Medium term						
With disk disease (n = 166)	67 (77.9%)	9 (10.5%)	10 (11.6%)	54 (67.5%)	14 (17.5%)	12 (15%)
Without disk disease (n = 160)	55 (78.5%)	9 (12.9%)	6 (8.6%)	49 (70%)	10 (14.2%)	11 (15.8%)
Long term						
With disk disease (n = 166)	64 (74.4%)	9 (10.5%)	13 (15.1%)	46 (57.5%)	16 (20%)	18 (22.5%)
Without disk disease (n = 160)	53 (75.8%)	11 (15.7%)	6 (8.6%)	44 (62.8%)	11 (15.8%)	15 (21.4%)

Note.—Data in parentheses are percentages. Short term = 1 week, medium term = 3 months, and long term = 6 months.

periganglionic steroid infiltration is the relief the periganglionic inflammation by ensuring recovery of the normal ganglioneural myelin sheath, and hence nerve function, at the disease site (16, 17). The O_2-O_3 gas mixture injected proximal to the root ganglion is thought to normalize the levels of cytokines and prostaglandins, increase superoxide dismutase levels, minimize reactive oxidant species, and improve local periganglionic circulation with a eutrophic effect on the nerve root (15, 18, 19). This effect was especially evident at short-term follow-up in patients without disk disease, roughly 80% of whom reported a clear improvement in symptoms; this observation demonstrating that both treatments rapidly relieve nondiskal pain. Our medium- and long-term results marginally favored O_2-O_3 treatment, especially in patients with painful disk disease.

Periganglionic steroid treatment by means of CT-guided paraspinal infiltration is an effective tool for the relief of root pain caused by spondylosis or disk herniation, but the effects appear to be short lived (25, 26). This was particularly true in patients in the disk-disease group, in whom the rate of excellent outcomes fell from 80% in the short term to 57.6% at long-term follow-up. A statistically significant trend, with a relatively smooth slope, was noted in patients with disk disease group treated with O_2-O_3 infiltration, in whom the rate of excellent outcomes decreased from 84.8% at short-term follow-up to 74.4% at long-term follow-up (P = .0021).

Furthermore, undesired severe reactions, such as arachnoiditis, meningitis, paraparesis, paraplegia, sensory disorders, bowel/bladder dysfunction, headache and epilepsy, after steroid administration should

also be considered (20–24). Although these major adverse effects were not encountered in our series, a certain percentage of the drug is nonetheless metabolized.

Our most interesting finding was the increase in the number of patient with disk disease (disk-induced pain) who reported an improvement in symptoms. This finding supports other evidence that O_2-O_3 infiltration affects not only the symptoms but also the cause of pain by accelerating the natural recovery mechanism of disk herniation (27).

Conclusion

To our knowledge, no biochemical evidence suggests short or long-term adverse effects linked to O_3 administration, and O_2-O_3 treatment has proved highly effective in relieving acute and chronic low back pain and sciatica. Therefore, we suggest the administration of the gas mixture as a first-choice treatment to replace epidural steroid infiltration to avoid surgery.

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