

ORIGINAL RESEARCH ARTICLE

Observational study on the effectiveness of oxygen-ozone treatment vs. pharmacological treatment in patients with chronic low back pain after previous spinal stabilization surgery

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Abstract

Persistent low back pain after spinal stabilization with instrumentation remains a frequent and clinically demanding condition. In many cases, pain persists despite pharmacological therapy and rehabilitation, limiting quality of life. Among emerging non-surgical options, oxygen–ozone (O₂–O₃) therapy has been proposed for its analgesic, anti-inflammatory, and neuromodulatory properties. This study aims to evaluate the clinical effectiveness of computed tomography (CT)-guided infiltrative O₂–O₃ treatment in patients with chronic low back pain following spinal fusion and to compare outcomes with those of standard pharmacological therapy within structured rehabilitative care. This observational retrospective study included 168 adult patients with low back pain persisting for more than six months after posterior spinal fusion with screws and plates. Group A (*n* = 72) received CT-guided paravertebral infiltrations of an O₂–O₃ gas mixture at 20 µg/mL, followed by individualized physiotherapy. Group B (*n* = 96) received a combination of pharmacological agents (oxycodone/paracetamol and pregabalin) alongside the same rehabilitative program. Clinical evaluation was performed at baseline (T0), 1 month (T1), and 6 months (T2) using the Visual Analog Scale (VAS) and the modified McNab scale. Group A showed a significant mean VAS reduction (>3 points) already at T1, with benefits maintained at T2. Functional recovery was rated as “good” or “excellent” in approximately 60% of cases. In contrast, Group B exhibited a transient response at T1, with VAS scores returning close to baseline at T2. Intergroup differences in both pain reduction and functional improvement were statistically significant (*p* < 0.001). CT-guided O₂–O₃ infiltrative therapy, integrated with physiotherapy, was associated with better clinical outcomes compared to pharmacological treatment alone in patients with persistent low back pain after spinal fusion. These findings suggest a potential role for O₂–

O₃ therapy within a multimodal treatment approach for selected post-surgical patients.

Keywords: Low back pain; Spondylolisthesis; O₂–O₃ therapy; Oxygen–ozone therapy; Computed tomography-guided injections; Interventional neuroradiology; Chronic post-surgical pain

1. Introduction

Low back pain, with or without radicular involvement (lumbosciatica), is one of the most common musculoskeletal conditions globally, with a lifetime prevalence of up to 80% in the general population. It is the leading cause of work absenteeism in industrialized countries, having a significant impact in terms of disability and overall healthcare costs.^{1,2}

Among the various causes of chronic low back pain, spondylolysis plays a significant role. It is a discontinuity of the vertebral neural arch—particularly in the region between the superior and inferior articular processes—which can be associated with spondylolisthesis, the anterior slippage of one vertebral body over the one below. The term “spondylolisthesis” was first introduced by Kilian in 1854, and today the most commonly used clinical classification is that of Meyerding, which quantifies the degree of slippage as a percentage relative to the underlying vertebral body (Figure 1).^{3,4} The Meyerding classification is the most widely used standard for assessing the extent of anterior vertebral body slippage in spondylolisthesis. It is based on the percentage of translation of the superior vertebral body

over the base of the vertebra below, measured on lateral radiographic projections.⁵

Grade I spondylolisthesis is often asymptomatic and incidentally identified. However, in a significant proportion of patients, it may manifest with chronic low back pain, sometimes accompanied by radicular symptoms. The clinical presentation may include low back pain of variable intensity, accentuation of lumbar lordosis, and, in more severe cases, functional limitations in daily activities. Diagnosis is based on a detailed medical history and thorough physical examination, supported by diagnostic imaging: lateral and oblique X-rays complemented by morphodynamic tests in flexion-extension and right-left bending, computed tomography (CT) and/or magnetic resonance imaging (MRI), which are essential tools to identify the degree of slippage, spinal stability, and any associated structural alterations.^{5–10} Initial treatment of low-grade spondylolisthesis and symptomatic spondylolysis is usually conservative, involving physiotherapy programs, sometimes in association with analgesic therapy.

In cases resistant to conservative treatment, surgical spinal stabilization may become necessary. Although surgery has long been considered the standard treatment, long-term clinical effectiveness remains variable, leading in recent years to growing interest in minimally invasive and conservative approaches.^{10–12}

The treatment of post-stabilization spinal pain represents a complex clinical challenge, requiring a multimodal and individualized assessment. Pain persistence may result from multiple factors: post-surgical scar fibrosis with perineural adhesions, pseudoarthrosis, articular overload above or below the stabilization, or possibly associated discopathies.^{13–17}

Severe epidural fibrosis is present in over 80% of patients with persistent pain following spinal surgery¹³, while symptomatic pseudoarthrosis can occur in up to 2.7% of cases within 10 years of the procedure.¹⁴ Adjacent segment disease affects up to 36% of patients in the long term¹⁷, contributing to the clinical complexity of these conditions.

The management of post-stabilization spinal pain requires a multimodal and individualized approach.

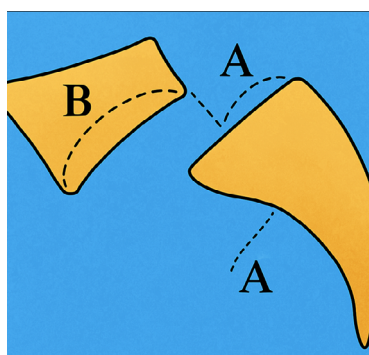


Figure 1. Schematic representation of the Meyerding classification. Grade I is characterized by minimal anterior vertebral displacement, not exceeding 33% of the anteroposterior diameter of the inferior vertebral body. Grade II denotes moderate slippage, ranging from 34% to 66%. Grade III corresponds to severe displacement, between 67% and 99%, often associated with marked disruption of vertebral alignment. Grade IV indicates complete anterior displacement, with 100% loss of contact between adjacent vertebral bodies. When the superior vertebra displaces entirely beyond the anterior border of the subjacent vertebra, the condition is termed spondyloptosis, representing a highly unstable scenario with complete vertebral body dislocation.

Conservative options include rehabilitation protocols aimed at restoring segmental functionality and stability, along with individualized pharmacological treatments, comprising analgesics, anti-inflammatory drugs, and medications for neuropathic pain.¹⁸ In addition to these strategies, minimally invasive procedures are playing an increasingly prominent role, including epidural or selective nerve root injections¹⁸, pulsed radiofrequency of the dorsal root ganglia^{18,19}, epiduroscopy for adhesion lysis¹⁹, and, in more complex cases, spinal cord stimulation, which has demonstrated efficacy in improving pain and quality of life.^{20,21}

Beyond these options, physiotherapeutic rehabilitation holds a crucial role, constituting one of the cornerstones of the post-surgical therapeutic pathway. Multiple randomized controlled trials and systematic reviews have shown that early, supervised exercise programs—ideally initiated within the first 4–12 weeks post-surgery—can significantly reduce pain, improve functional disability, and promote global recovery of dynamic spinal stability.^{22–24} Contemporary rehabilitation protocols incorporate muscle-strengthening exercises, motor control retraining, proprioceptive work, and cognitive-behavioral interventions aimed at reducing fear of movement (kinesiophobia) and improving psychological adaptation to residual chronic pain.^{24–26}

Thus, the integration of personalized physiotherapy not only improves primary clinical outcomes but also helps prevent recurrence and reduces the risk of chronic pain, ultimately optimizing patients' long-term quality of life. These techniques, well-tolerated and repeatable, allow targeted action on pain generators, providing significant benefits to patients.

Among various therapeutic strategies, oxygen–ozone (O₂–O₃) therapy has gained increasing attention and adoption. Introduced in the 1980s for the treatment of discogenic pain, paravertebral or intraforaminal infiltration of an oxygen–ozone mixture has shown encouraging results in the management of low back pain and lumbosciatica not only of discal origin, but also extradiscal (facet joint syndromes, inter- and intra-articular synovitis, spondylolysis, and spondylolisthesis). The mechanism of action identifies controlled modulation of oxidative stress as the primary biological trigger: through the transient generation of reactive oxygen species (ROS) and lipid oxidation products (LOPs), ozone induces activation of the Nuclear factor erythroid 2–related factor 2/Kelch-like ECH-associated protein 1/antioxidant response element (Nrf2/Keap1/ARE) pathway, resulting in increased expression of cytoprotective, antioxidant, and anti-inflammatory genes.^{27–38}

At the same time, inflammatory pathways mediated by nuclear factor-kappa B (NF-κB) are modulated, and vasomodulatory and microcirculatory effects are promoted through increased expression of inducible nitric oxide synthase (iNOS) and improved tissue oxygen bioavailability. These synergistic effects lead to reduced periradicular edema, enhanced tissue trophism, and significant pain relief.^{39–48}

Numerous studies have reported therapeutic success rates ranging from 70% to 85% in patients with chronic low back pain, with or without radicular involvement of discogenic origin.^{1–12,48–64} However, the application of O₂–O₃ therapy in patients who have already undergone spinal stabilization surgery remains scarcely documented, highlighting the need for further evaluation in this specific clinical subgroup. Recent evidence indicates that the combination of physiotherapy and O₂–O₃ injections can significantly reduce pain and disability, with marked and long-lasting effects, even in subacute cases, potentially due to the synergy between the biochemical action of ozone and the neuromuscular activation promoted by rehabilitation.^{65–67} These findings provide a strong rationale for investigating whether similar benefits may be observed in patients with persistent pain after spinal stabilization.

The objective of the present study is therefore to evaluate the clinical effectiveness of infiltrative O₂–O₃ treatment, compared with standard pharmacological therapy, in a selected sample of 72 patients with chronic low back pain persisting for more than 6 months following vertebral arthrodesis with screws and metal plates. Specifically, 58 patients presented with Grade I spondylolisthesis according to the Meyerding classification, while the remaining 14 underwent surgery based on clinical decision despite the absence of spondylolisthesis, due to possible isthmic lysis and documented vertebral instability. In all cases included in the study, the surgical procedure did not involve the placement of interbody cages.

The research hypothesis underlying the present study is that CT-guided paravertebral O₂–O₃ infiltration, combined with a structured physiotherapy program, results in a significantly greater clinical improvement—both in pain reduction and functional recovery—compared to pharmacological treatment combined with the same physiotherapy program, in patients with persistent chronic low back pain following spinal stabilization surgery.

2. Materials and methods

2.1. Study design and population

The study used a retrospective, observational, and comparative design, covering the period from January

2022 to April 2025. The aim of the study is to evaluate the effectiveness of O₂–O₃ therapy, in combination with a targeted rehabilitation physiotherapy program, in the treatment of chronic low back pain persisting for more than six months in patients who had previously undergone spinal arthrodesis using screw and plate stabilization (Figures 2 and 3). The clinical outcomes of this treatment (Group A: O₂–O₃ therapy + physiotherapy) were compared with those of a group (Group B) treated with analgesic pharmacological therapy combined with rehabilitation physiotherapy, in order to investigate the potential added value of the infiltrative O₂–O₃ mixture approach in the management of chronic post-surgical low back pain. Clinical evaluations were conducted at three time points: baseline (T0), 1 month (T1), and 6 months (T2).

The study was conducted and reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines, where applicable to the study design.

2.2. Patient allocation and eligibility criteria

A total of 168 patients were included in the final analyzed cohort. Among them, 72 patients (Group A; mean age: 58.4 ± 13.6 years; 42 females, 30 males) underwent CT-guided O₂–O₃ therapy, while 96 patients (Group B; mean age: 56.1 ± 16.2 years; 54 females, 42 males) received pharmacological treatment. Initially, 104 patients had been allocated to pharmacological treatment. However, 8 patients who experienced treatment-related adverse effects (constipation, headache, nausea and vomiting) discontinued therapy before the final eligibility assessment and were therefore excluded from the analyzed cohort.

All patients had previously undergone spinal stabilization surgery with screw and plate implantation and continued to experience chronic low back pain (Figures 2 and 3).

Patients were allocated to two groups (Group A: O₂–O₃ therapy plus physiotherapy; Group B: pharmacological therapy plus physiotherapy) without randomization. Given the retrospective design, pre-existing cohorts were analyzed, reflecting treatments administered according to individualized clinical indications established by a multidisciplinary team. Treatment allocation was based on clinical judgment, previous therapeutic response, and patient preference, in agreement with the treating physician. This approach was chosen to reflect real-world clinical practice.

To improve comparability between groups, the following criteria were applied:

(i) Inclusion criteria:

- Age > 18 years
- Chronic low back pain lasting > 6 months after spinal stabilization
- Availability of at least 6 months of follow-up
- Signed informed consent for the use of anonymized clinical data

(ii) Exclusion criteria:

- Documented malposition of pedicle screws
- Evidence of active osteolysis
- Incomplete follow-up data

2.3. Treatment protocols and rehabilitation program

Group A patients were treated with CT-guided (Supria 16, Hitachi Medical Systems, Japan) paravertebral infiltrations of an O₂–O₃ gas mixture, without concomitant pharmacological therapy during the infiltration phase. Following completion of the infiltrative treatment, all patients were referred to a structured physiotherapy program consisting of individualized functional rehabilitation over a period of six months. Etiological factors responsible for lumboradicular symptoms in patients from Group A included: pseudarthrosis of the stabilized segment ($n = 10$; 13.9%), periradicular scar fibrosis ($n = 34$; 47.2%), functional overload on non-stabilized facet joints ($n = 20$; 27.8%), and in 8 patients (11.1%) the presence of protrusions or herniated discs was identified as the cause of residual pain symptoms.

Group B patients received pharmacological therapy combined with the same rehabilitative program from the outset. The therapeutic protocol included the combined administration of the following:

- Oxycodone/paracetamol: A fixed-dose combination of oxycodone hydrochloride 5 mg + paracetamol 325 mg per tablet, administered four times daily (every 6 h), with individual dose titration based on pain control.
- Pregabalin: 75 mg oral suspension, administered twice daily.

This combination was selected to reflect a real-world multimodal pharmacological strategy for chronic post-surgical low back pain, where nociceptive and neuropathic components may coexist. Oxycodone/paracetamol was used to address the nociceptive component, while pregabalin was included to target neuropathic or lumboradicular pain features, consistent with commonly adopted clinical pain-management protocols.^{14,18,20} Treatment could be adjusted or discontinued in case of adverse effects.

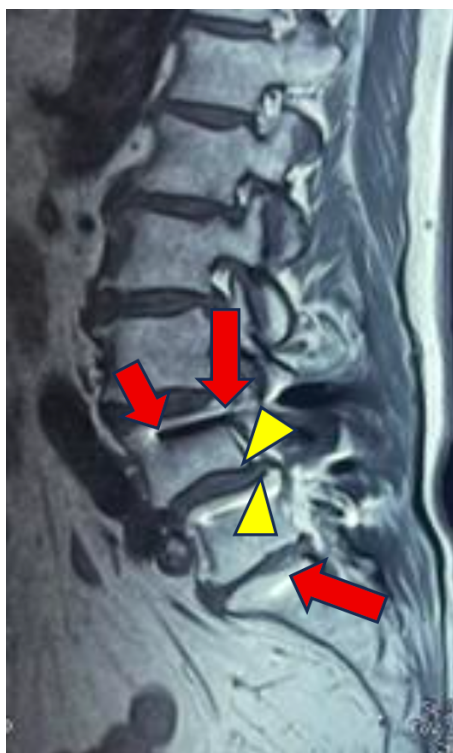


Figure 2. Sagittal magnetic resonance imaging: vertebral stabilization from L4 to S1 with metal screw-plate system (red arrows) in Grade I Meyerding spondylolisthesis of L4 over L5 (yellow arrowheads)

Pharmacological therapy and physiotherapy were administered concurrently for a minimum of 30 days, with subsequent continuation or adjustment based on individual clinical evolution. The physiotherapy protocol was identical in both groups and consisted of three weekly sessions (45–60 min) for at least four weeks. The program included postural re-education, core stabilization, proprioceptive neuromuscular facilitation, passive and active mobilization, and targeted muscle stretching. Adjunctive therapies (e.g., low-intensity laser or infrared thermotherapy) were applied when clinically indicated.

Pharmacological treatment and the physiotherapy program were carried out concurrently for a minimum duration of 30 days. In the following months, patients continued with personalized physiotherapy protocols, with potential continuation or adjustment of pharmacological therapy depending on individual clinical evolution.

In all patients (Groups A and B), the initial physiotherapy program consisted of three weekly sessions lasting 45–60 min each, for a minimum period of four

weeks. The treatment was administered by licensed physiotherapists, following a structured protocol with common components, and allowing for personalization based on individual functional assessment. The protocol included:

- Postural re-education and core stabilization exercises aimed at improving spinal alignment and muscle control;
- Proprioceptive neuromuscular facilitation techniques to enhance coordination and neuromuscular response;
- Passive and active mobilization to promote lumbar segmental mobility;
- Targeted stretching of the lumbar paravertebral, gluteal, and hamstring muscles; and
- Adjunctive therapies, such as low-intensity laser or infrared thermotherapy, were used when clinically indicated (Figure 4).

2.4. Clinical assessment and follow-up

All patients underwent clinical evaluation at baseline and during follow-up using standardized outcome measures. Two standardized tools were used to assess treatment effectiveness⁶¹:

- Visual Analog Scale (VAS): A validated psychometric tool widely used for measuring perceived pain intensity. It consists of a 10 cm straight line with no intermediate numeric indications, where the endpoints are labeled “0 = no pain” and “10 = worst imaginable pain.” The patient was asked to mark a point on the line that best represents their current level of pain. The VAS was administered at three time points (T0, T1, and T2) to monitor the course of pain symptoms.
- Modified McNab scale: Used for the subjective assessment of functional outcomes, this scale provides a simple yet clinically meaningful classification of perceived improvement, divided into three categories:
 - (i) Excellent: Complete resolution of pain and full return to pre-symptom daily activities;
 - (ii) Good or satisfactory: More than 50% reduction in pain compared to baseline;
 - (iii) Fair or poor: Partial reduction in pain of less than 50%, with persistent functional limitations.

2.5. O₂–O₃ infiltration procedure

The O₂–O₃ treatment was administered at the vertebral level previously subjected to stabilization surgery, following local skin anesthesia with ethyl chloride spray. CT guidance was used to confirm the correct positioning of the spinal needle in the periganglionic region (Figure 5).

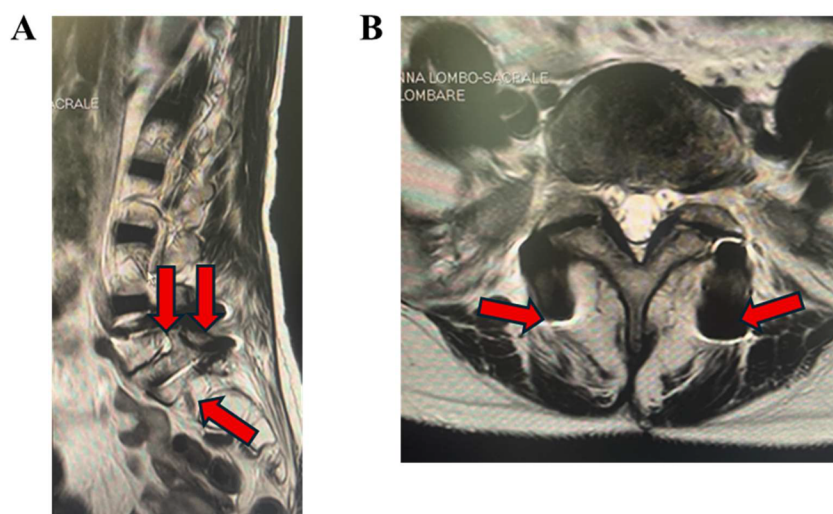


Figure 3. Magnetic resonance imaging (MRI) in multiple planes. (A) Sagittal MRI: Vertebral stabilization at L5–S1 (arrows). (B) Axial MRI: Scan at the L5–S1 disc level showing a mild bilateral median–paramedian protrusion of the annulus, with greater focality in the left intraforaminal region (arrows).

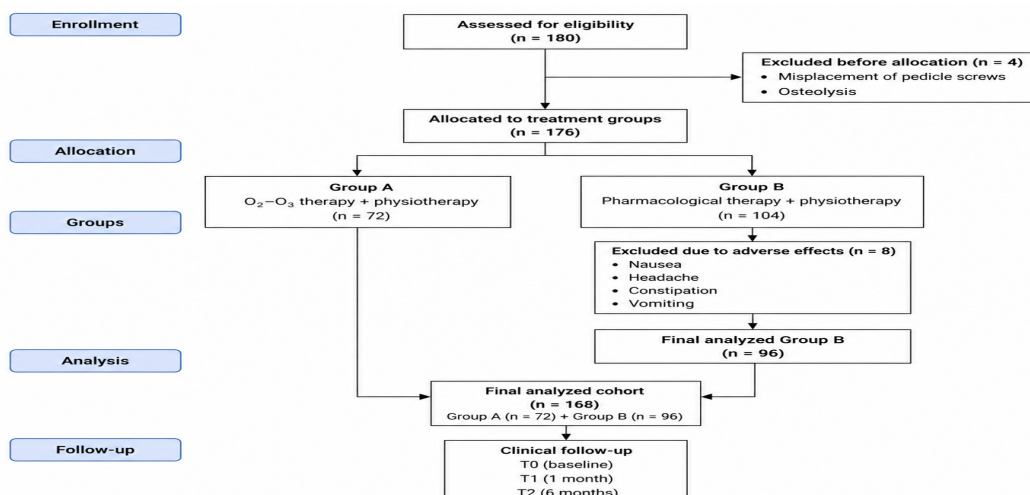


Figure 4. Flowchart of the study design, illustrating the process of patient selection, allocation to treatment groups, and clinical follow-up

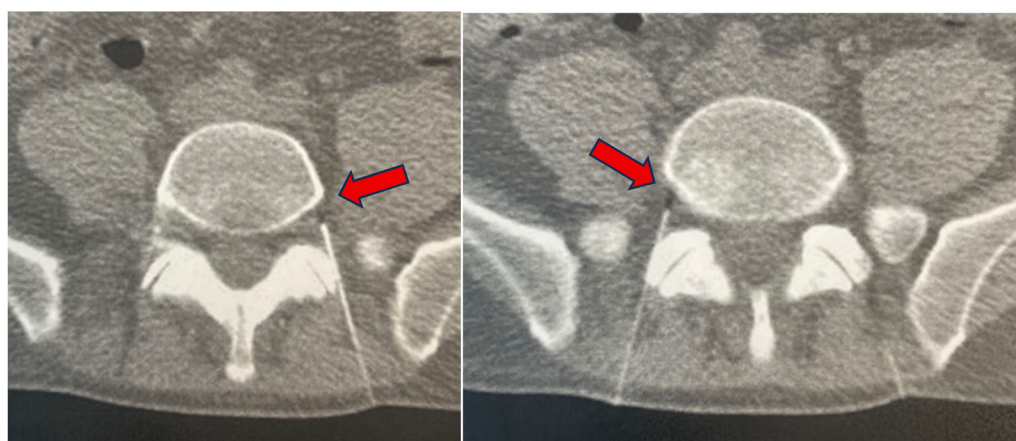


Figure 5. Computed tomography verification of correct needle placement in the periganglionic region (arrows)

A total of 3–4 cm³ of an O₂–O₃ gas mixture at 20 µg/mL was injected as a single shot in the periganglionic region. The needle was then withdrawn by a few centimeters, and an additional 3–4 cm³ of the gas mixture was injected into the paravertebral musculature and over the articular mass. CT guidance was used throughout the procedure to confirm the correct distribution of the gas mixture (Figures 6 and 7).

The O₂–O₃ gas mixture was produced with the Alnitec OZO 2 Futura PLUS generator (Alnitec Srl, Italy), a Class II medical device with Conformité Européenne (CE; European Conformity) marking, equipped with a high-precision Alnitec photometer featuring fully automated controls (Alnitec Srl) for automatic calibration and precise concentration control. The system, with no manual adjustments, uses medical-grade oxygen and generates ozone from 1 to 100 µg/mL, with 10 programmable sequences. It features an integrated catalyst for neutralizing residual ozone and operates at a supply voltage of 230 V at 50 Hz. All treatments were carried out at the standard concentration of 20 µg/mL, in accordance with the guidelines of the Italian Federation of Oxygen–Ozone Therapy.⁶⁸

No adverse events related to O₂–O₃ were observed in our sample. This finding is consistent with the literature, as complications associated with O₂–O₃ therapy are extremely rare and, in the vast majority of cases, attributable to procedural errors (malpractice).^{48–50} The use of CT guidance and the application of standardized concentrations and volumes are key factors in ensuring treatment safety.

Patients in whom the pedicle screws were deemed to be improperly positioned (Figure 8) were excluded from the study and referred for specialist reassessment. Additionally, one patient presenting with evident bone resorption around the pedicle screws (Figure 9) was also excluded.

Assessments were performed at baseline (T0), 1 month (T1), and 6 months (T2) after treatment initiation to monitor clinical progression and compare the medium-term effectiveness of the two treatment strategies (Figure 4). In patients who did not achieve satisfactory clinical improvement at one month or who experienced significant adverse effects, adjunctive therapy with serotonin–norepinephrine reuptake inhibitors was introduced. These patients also underwent neurosurgical reassessment to evaluate potential indications for further interventions.

2.6. Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 29.0 (IBM Corp., United States of America).

Continuous variables were summarized as means with 95% confidence intervals (CIs), while categorical variables were reported as frequencies and percentages. The normality of VAS score distributions was assessed using the Shapiro–Wilk test.

As VAS scores were not normally distributed, within-group changes over time were analyzed using non-parametric tests. The Friedman test was used to assess overall differences across the three time points (T0, T1, and T2), followed by Wilcoxon signed-rank tests for pairwise comparisons. Between-group comparisons of VAS scores were performed using the Mann–Whitney *U* test.

Categorical outcomes based on the modified McNab scale were compared using the Chi-square test or Fisher's exact test, as appropriate. Effect sizes were calculated using the *r* coefficient for non-parametric comparisons and partial eta squared (η^2) for repeated-measures analyses. A repeated-measures ANOVA with the Greenhouse–Geisser correction was also performed as a robustness analysis to evaluate temporal trends in pain scores. Statistical significance was set at $p < 0.05$, two-tailed. A post hoc power analysis was conducted using G*Power 3.1.9.7 (Heinrich Heine University Düsseldorf, Germany), assuming $\alpha = 0.05$ and a moderate effect size (Cohen's $d = 0.5$). The available sample size provided statistical power greater than 80%, supporting the adequacy of the study to detect clinically meaningful between-group differences.

3. Results

According to the modified McNab scale, in Group A (O₂–O₃ therapy + physiotherapy), 43 out of 72 patients (59.7%; 95% CI: 47.4–71.1%) reported a “good” or “excellent” outcome at 1 month (T1), while 37 out of 72 patients (51.4%; 95% CI: 39.0–63.6%) maintained this level of improvement at 6 months (T2). The change over time was statistically significant ($\chi^2 = 12.35$, $p = 0.015$).

In Group B (pharmacological therapy + physiotherapy), 24 out of 96 patients (25.0%; 95% CI: 17.0–34.3%) reported “good” or “excellent” outcomes at T1, and 25 out of 96 (26.0%; 95% CI: 18.0–35.1%) at T2 (Table 1).

Pain intensity analysis (VAS) in Group A showed a reduction from a mean of 7.5 (95% CI: 7.3–7.7) at baseline (T0) to 4.2 (95% CI: 4.0–4.4) at T1, with partial maintenance at T2 (mean 4.6; 95% CI: 4.4–4.8) (Table 1). The Friedman test confirmed a statistically significant variation over time ($\chi^2 = 128.4$, $p < 0.001$). Pairwise comparisons (Wilcoxon signed-rank test) showed significant differences between T0 and T1 ($p < 0.001$), T1 and T2 ($p = 0.004$), and T0 and T2 ($p < 0.001$).

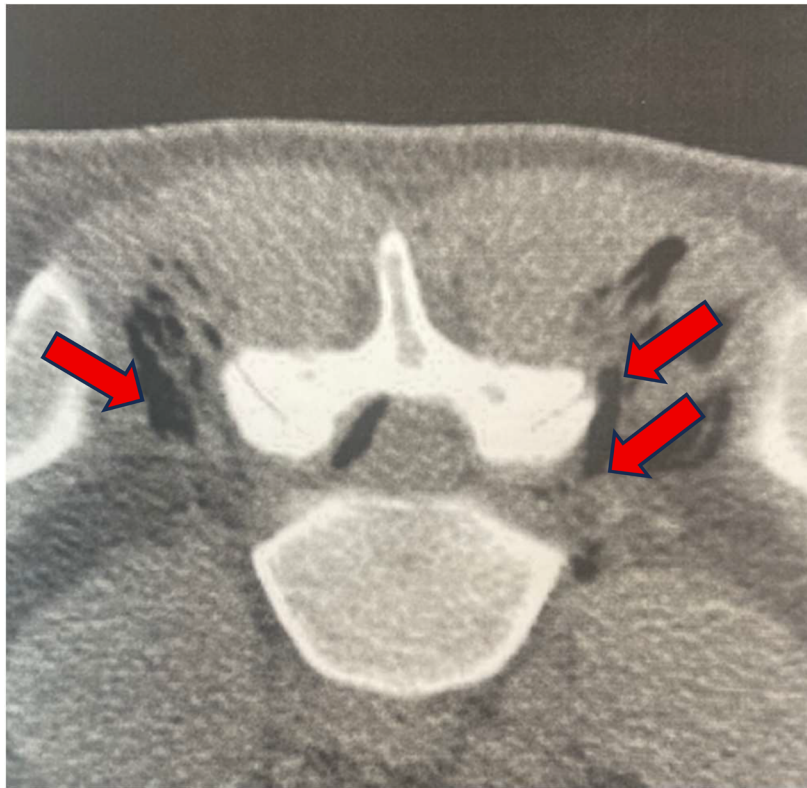


Figure 6. Axial computed tomography scan confirming the distribution of the O₂-O₃ gas mixture (arrows)

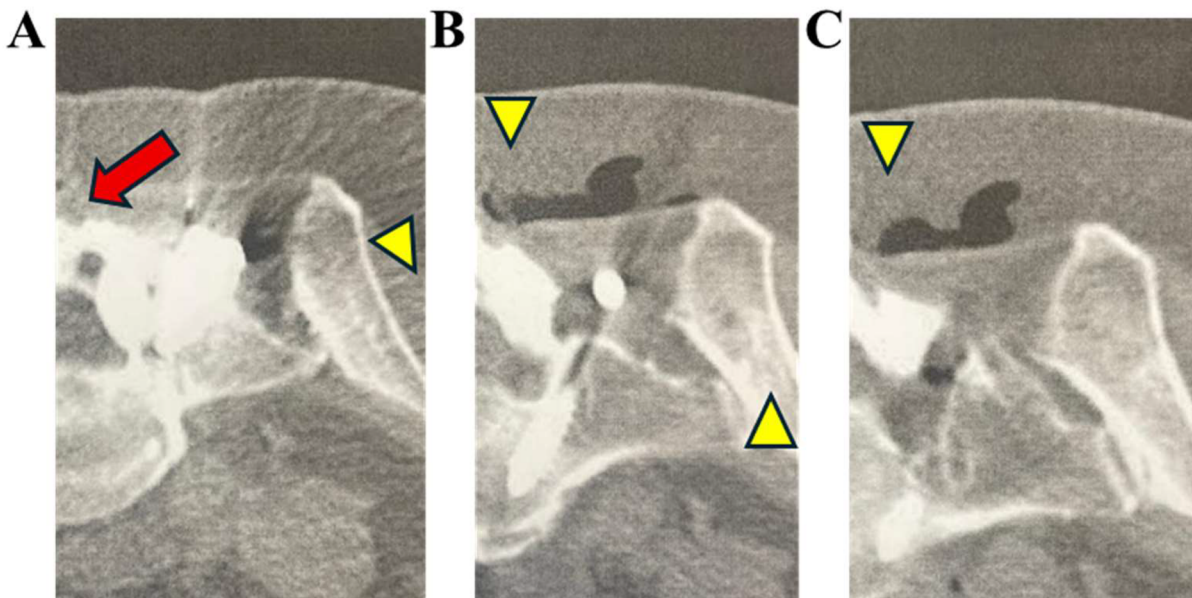


Figure 7. Patient with chronic low back pain following spinal stabilization, complicated by left-sided sciatica. Electromyographic examination showed chronic neurogenic impairment in the S1 left distribution territory. (A) Low-dose parenchymal algorithm computed tomography (CT) scan confirming needle placement (arrow). (B-C) CT control scans documenting the distribution of the gas mixture (arrowheads).

In Group B, VAS scores decreased from a mean of 7.4 (95% CI: 7.2–7.6) at T0 to 5.3 (95% CI: 5.1–5.5) at T1, followed by an increase to 6.2 (95% CI: 6.0–6.4) at T2 (Table 1; Figure 10). Pairwise comparisons showed differences between T0 and T1 ($p = 0.003$) and between T1 and T2 ($p = 0.021$), whereas no clear difference was observed between T0 and T2 ($p = 0.146$). Repeated-measures ANOVA indicated an overall temporal effect ($F = 55.12, p < 0.001$).

At 6 months, VAS values in Group B approached baseline levels, whereas Group A maintained a lower mean pain intensity (Figures 10 and 11). The mean VAS reduction in Group A (–3.3 points at T1 and –2.9 at T2 compared to baseline) exceeded the minimal clinically important difference for chronic low back pain, typically estimated between 1.5 and 2.0 points on a 0–10 scale.^{69–71}

4. Discussion

The findings of the present study clearly underscore the clinical efficacy of O₂–O₃ therapy in managing chronic low back pain persisting after spinal stabilization surgery. The comparison with the control group (Group B), which received only pharmacological treatment, revealed significant differences in both pain intensity reduction (as measured by the VAS) and functional recovery (as assessed by the modified McNab scale). A mean reduction of more than 3 points on the VAS, already observed one month after treatment and sustained at six months, along with 59.7% of patients reporting “good” or “excellent” outcomes, indicates a strong and lasting therapeutic impact.

The physiological rationale underlying this efficacy is supported by recent advancements in molecular

biochemistry. Ozone, a highly reactive triatomic molecule, does not act directly on cells but induces an adaptive response in the biological microenvironment via controlled oxidative stress. This phenomenon, referred to as oxidative hormesis, leads to the generation of ROS and LOPs, which serve as intracellular second messengers.^{27–38}

The key mechanism behind O₂–O₃ therapy’s effectiveness lies in the activation of the Nrf2/Keap1/ARE pathway, which is recognized as the central regulator of the cytoprotective antioxidant response. Under baseline conditions, the transcription factor Nrf2 is sequestered by Keap1, a cytosolic protein that facilitates its proteasomal degradation. ROS and LOPs generated by ozone modify thiol residues on Keap1 cysteines, triggering conformational changes that release Nrf2 and allow its nuclear translocation. Once in the nucleus, Nrf2 binds to ARE and promotes the transcription of key antioxidant and anti-inflammatory genes, including glutathione peroxidase, superoxide dismutase, catalase, heme oxygenase-1 (HO-1), and NAD(P)H quinone dehydrogenase 1 (NQO1). The result is a robust endogenous enhancement of cellular defenses, a reduction in systemic oxidative stress, and suppression of pro-inflammatory pathways mediated by NF- κ B, leading to decreased levels of cytokines such as interleukin (IL)-1 β , IL-6, and tumor necrosis factor-alpha (TNF- α). Moreover, Nrf2 pathway activation is known to interact with the hypoxia-inducible factor 1-alpha (HIF-1 α) pathway, which is responsible for cellular adaptation to hypoxia by promoting angiogenesis, erythropoiesis, and improved tissue perfusion—effects of particular relevance in the post-surgical vertebral context. The hormetic response elicited by O₂–O₃, when properly dosed (10–40 μ g/mL), does not induce oxidative damage. Instead, it supports the regulated

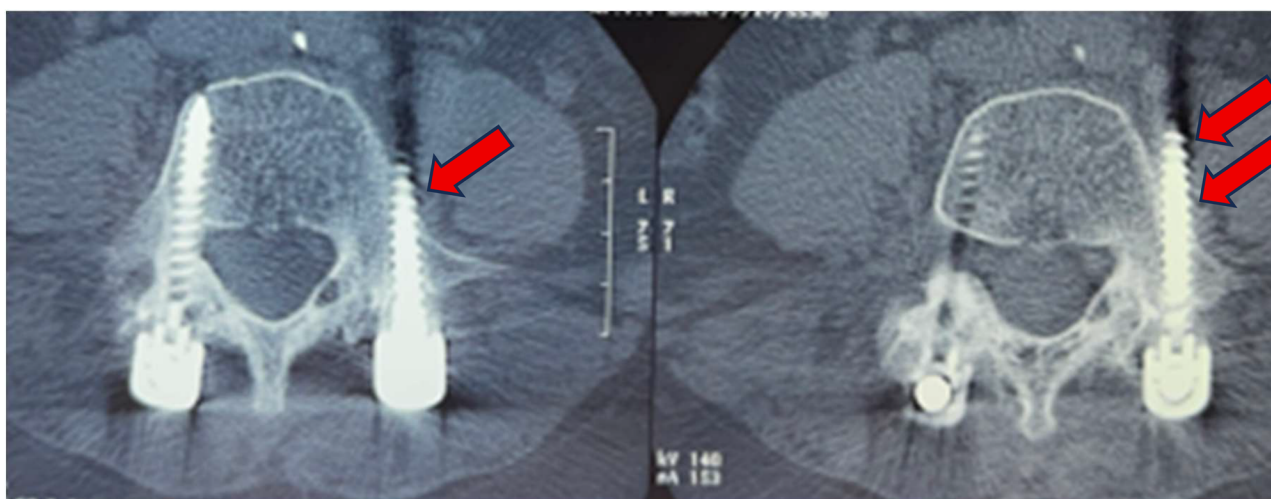


Figure 8. Computed tomography imaging demonstrates lateral misplacement of the left pedicle screw (arrows), leading to the exclusion of the patient from the study and prompting referral for further specialist evaluation

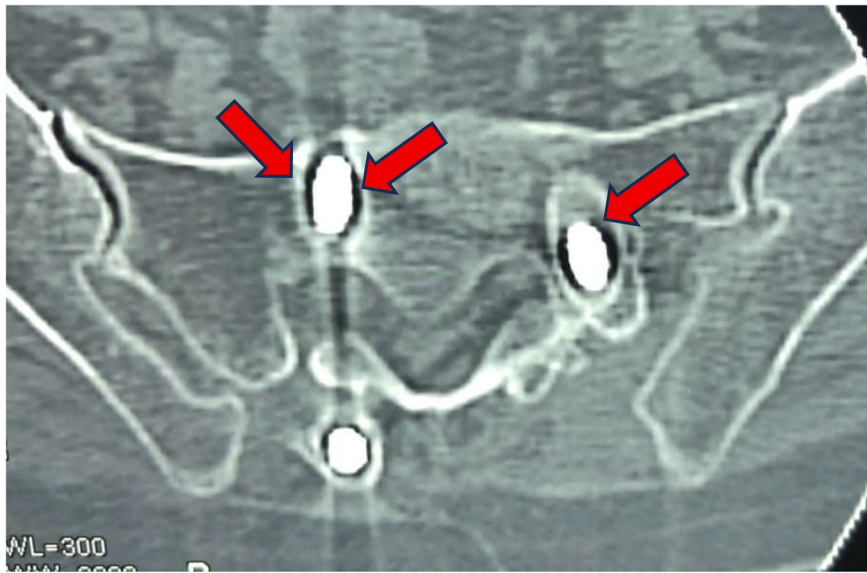


Figure 9. Patient excluded from the study due to the presence of a radiolucent rim of osteolysis around the S1 pedicle screws (arrows)

Table 1. Clinical outcomes (VAS and modified McNab scale) at T0, T1, and T2 in both treatment groups

Time point	VAS		Modified McNab scale improvement (%)	
	Group A	Group B	Group A	Group B
T0	7.5 (7.3 – 7.7)	7.4 (7.2 – 7.6)	0	0
T1	4.2 (4.0 – 4.4)	5.3 (5.1 – 5.5)	59.7 (47.4– 71.1)	25.0 (17.0 – 34.3)
T2	4.6 (4.4 – 4.8)	6.2 (6.0 – 6.4)	51.4 (39.0 – 63.6)	26.00 (18.0 – 35.1)

Notes: Group A: O₂–O₃ + physiotherapy; Group B: Pctharmacological therapy + physiotherapy.
Abbreviation: VAS: Visual Analog Scale.

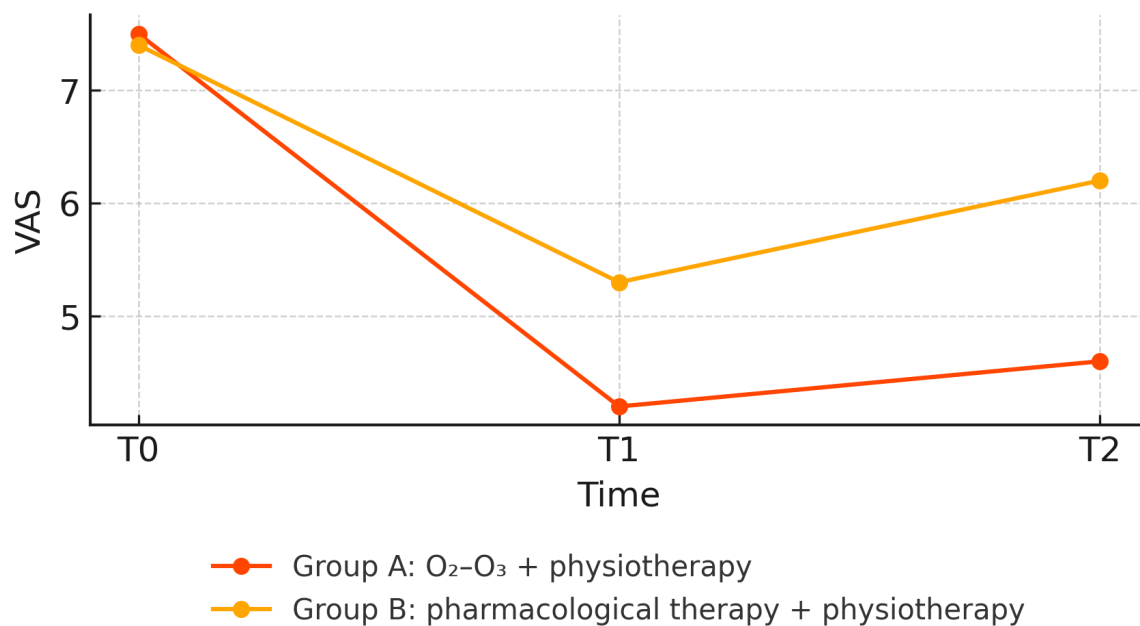


Figure 10. Perceived pain progression (Visual Analog Scale [VAS])

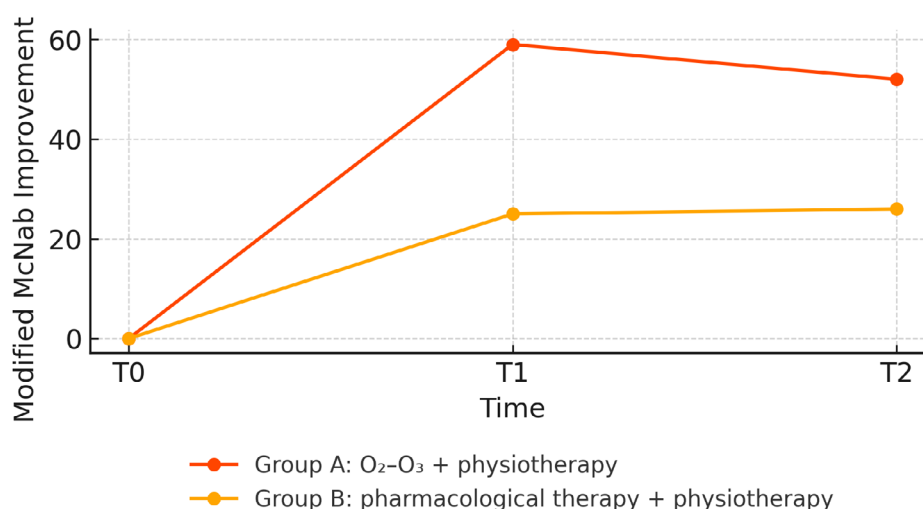


Figure 11. Percentage of functional improvement according to the modified McNab scale

production of 4-hydroxynonenal (4-HNE), a bioactive aldehyde that functions as a physiological signaling molecule and modulates systemic redox homeostasis. This mechanism also accounts for the absence of hematologic toxicity (hemolysis < 1.2%) and the favorable impact on erythrocyte metabolism, including increased ATP and 2,3-diphosphoglycerate levels, which facilitate oxygen release to ischemic tissues. Additionally, O₂–O₃ therapy positively influences autophagy—a key process in maintaining cellular homeostasis—via Nrf2-mediated upregulation of P62 and inhibition of mammalian target of rapamycin (mTOR). This effect has been demonstrated in animal models and may contribute to tissue regeneration in chronic inflammatory conditions.^{27–38}

In summary, O₂–O₃ therapy should not be considered merely a symptomatic intervention, but rather a systemic modulator exerting pleiotropic effects: restoring redox balance, regulating inflammation, improving tissue perfusion, and facilitating functional recovery. Its demonstrated efficacy in post-surgical spinal patients unresponsive to conventional approaches aligns well with the biochemical mechanisms described.^{27–38}

This study is not without limitations. It was conducted retrospectively on real-world clinical data, without randomized allocation to treatment groups. This design, however, reflects the need to respect individualized therapeutic pathways already established at the time of clinical indication, with treatment decisions made by a multidisciplinary team according to each patient's specific characteristics. While the observational, non-randomized design and the absence of a placebo or rehabilitation-only control group preclude definitive causal inference, the

application of strict eligibility criteria and the comparable baseline characteristics between groups help to mitigate potential selection bias.

Despite these constraints, the results are consistent and robust, strongly suggesting a tangible clinical benefit and providing a solid rationale for future prospective, randomized, controlled trials. Such studies, ideally with extended follow-up, will be essential to confirm these findings, further minimize bias, and better define the long-term stability and durability of therapeutic outcomes.

5. Conclusion

The collected data suggest that paravertebral administration of O₂–O₃ under CT guidance may represent an effective, safe, and durable therapeutic option for the management of chronic low back pain following spinal stabilization surgery. Compared to standard pharmacological therapy, O₂–O₃ treatment was associated with clinically significant superiority in both pain reduction and perceived functional improvement. Within the limitations of this observational study, O₂–O₃ therapy can be considered a promising integrative approach in the multimodal management of chronic post-surgical low back pain, particularly when conventional therapies prove ineffective or poorly tolerated. Future prospective, randomized, and controlled studies with long-term follow-up are warranted to further validate these findings and establish standardized protocols for their application in this specific clinical context.

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Conflict of interest

The authors declare no conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical approval and consent to participate

This retrospective observational study was conducted in accordance with the principles of the Declaration of Helsinki. Given the retrospective and observational design of the study, based on anonymized clinical data collected during routine clinical practice, no formal request for ethical committee approval was submitted. All patients provided written informed consent prior to inclusion in the study to undergo the planned treatments and to allow the use of their anonymized clinical data for research purposes.

Consent for publication

All patients provided written informed consent for publication of anonymized data and images included in this manuscript.

Availability of data

The datasets generated and/or analyzed during the current study are not publicly available due to patient confidentiality and applicable privacy regulations, but may be made available from the corresponding author on reasonable request.

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