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Short Communication

Ozone therapy versus surgery for lumbar disc herniation: A randomized double-blind controlled trial☆

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ABSTRACT

Objectives: Surgery is the treatment of choice for symptomatic disc herniation after conservative management. Several studies have suggested the potential utility of intradiscal ozone infiltration in this pathology. The aim of this trial was to compare intradiscal ozone infiltration vs. oxygen infiltration vs. surgery.
Design and interventions: This was a randomized, double-blinded, and controlled trial in patients on a waiting list for herniated disc surgery. There were three treatment groups: surgery; intradiscal ozone infiltration (plus foraminal infiltration of ozone, steroids, and anesthetic); intradiscal oxygen infiltration (plus foraminal infiltration of oxygen, steroids, and anesthetic).
Main outcome measures: The requirements for surgery.
Results: Five years after the treatment of the last recruited patient (median follow-up: 78 months), the requirement for further surgery was 20 % for patients in the ozone group and 60 % for patients in the oxygen group. 11 % of patients initially treated with surgery also required a second surgery. Compared to the surgery group, the ozone group showed: 1) significantly lower number of inpatient days: median 3 days (interquartile range: 3–3.5 days) vs. 0 days (interquartile range: 0–1.5 days), $p = 0.012$; 2) significantly lower costs: median EUR 3702 (interquartile range: EUR 3283–7630) vs. EUR 364 (interquartile range: EUR 364–2536), $p = 0.029$.
Conclusions: Our truncated trial showed that intradiscal ozone infiltrations decreased the requirements for conventional surgery, resulting in decreased hospitalization durations and associated costs. These findings and their magnitude are of interest to patients and health services providers. Further validation is ongoing.

1. Introduction

According to the 2010 Global Burden of Disease Study, low back pain (LBP) is the sixth most common disease contributing to the global burden of disease, and significantly reduces quality of life.[1] In 2017, globally, LBP remained as the most common musculoskeletal problem and the most important cause of disability and absenteeism from work, with global years lived with disability of 64.9 million.[2] LBP is also responsible for a huge medical and socio-economic cost, estimated in 2016 in United States at 134.5 billion US$.[3] LBP, with or without sciatic nerve involvement, affects approximately 70%–80% of the population at least once in their lifetimes,[4] with a prevalence of 7.5 % in 2017.[2]

The most common pathogenesis of LBP with nerve root compression is lumbar disc herniation (LDH). After refractory conservative management, the treatment of choice for LDH is surgery (discectomy or microdiscectomy), which is indicated in patients with intolerable pain,

☆ The authors obtained approval from the local Research Ethics Review Committee of Las Palmas (Spain) for this study and the above-mentioned clinical trials.

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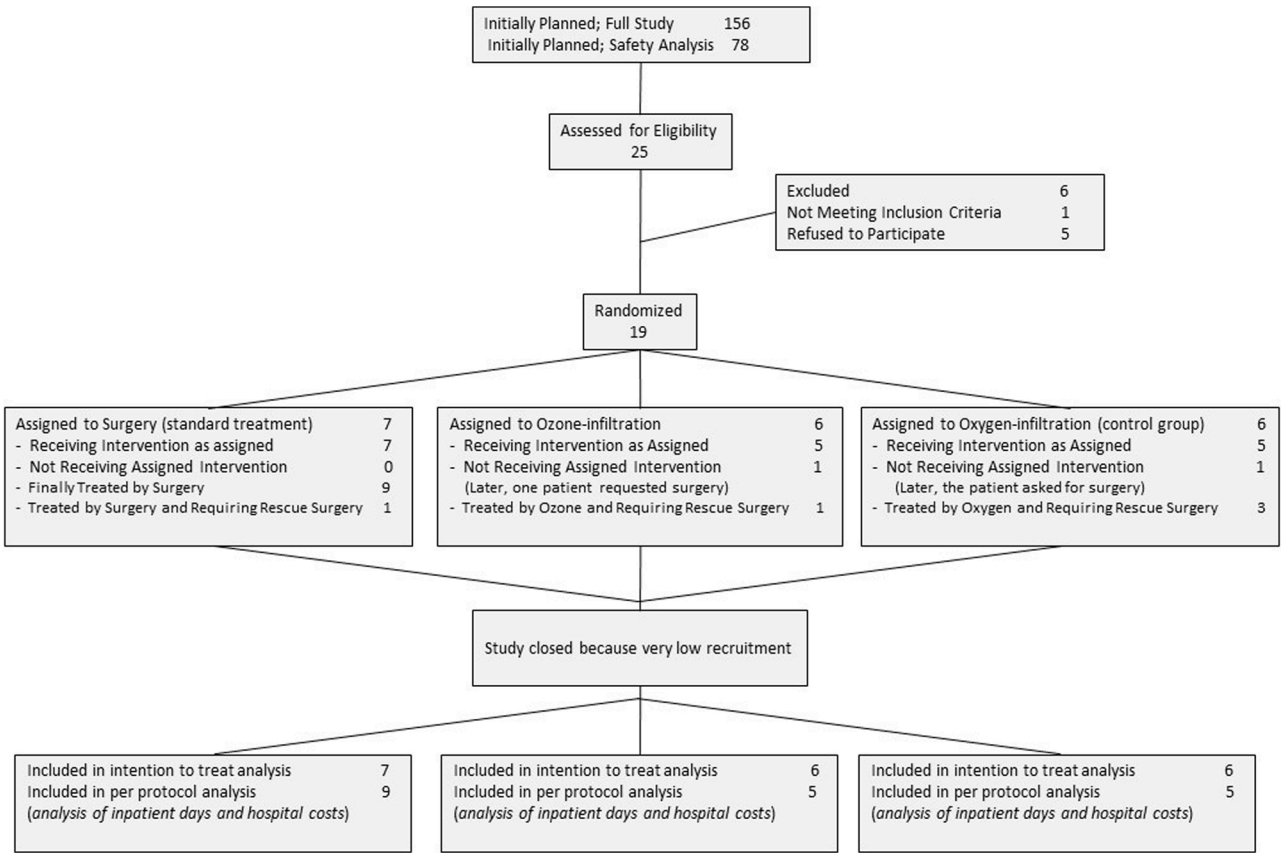

Fig. 1. CONSORT flow diagram of the truncated study.

Table 1
Results summary and statistical analyses.

	Surgery arm	Ozone arm	Oxygen arm	Surgery vs. Ozone
Number of patients				
ITT	7	6	6	
PP	9	5	5	
Hospitalization days				
ITT	3 (3–3)	0 (0–3)	2.5 (0–6)	$P = 0.051$
PP	3 (3–3.5)	0 (0–1.5)	2 (0–3.5)	$P = 0.012$
Cost (EUR)				
ITT	3702 (3336–6343)	364 (364–3596)	3729 (364–5353)	$P = 0.022$
PP	3702 (3283–7630)	364 (364–2536)	3552 (364–4035)	$P = 0.029$
Days from enrolment to treatment		**Infiltration arms**		
ITT	81 (46–127)	15 (9–27)		$P = 0.005$
PP	81 (51–144)	12 (8–25)		$P < 0.001$

ITT: intention to treat analysis; PP: per protocol analysis. Surgery arm: discectomy or microdiscectomy. Ozone (O2O3) arm: O2O3 infiltration + steroids + anesthetic. Oxygen (O2) arm: O2 infiltration + steroids + anesthetic. After randomization, one patient from the O2O3 arm and another from the O2 arm requested surgery and were treated accordingly but without infiltration. Compared to discectomy and microdiscectomy, the shorter period from enrollment to treatment in the intradiscal infiltration groups was related to the easier planning for the minimally invasive outpatient procedure compared with the standard surgery approach. Values of $P < 0.05$ were considered statistically significant. Differences between "O2 and O2O3" arms and "O2 and surgery" arms were not statistically significant, and the *p*-values have not been presented in the Table 1.

progressive neurologic deficits or cauda equina syndrome.[5] Nonetheless, the success rate of surgery tends to decrease on long-term follow-up due to the onset of symptoms of failed back surgery syndrome, and additional conservative methods are required. Oxygen-ozone (O2O3) therapy has been revealed to have a substantial pain relief effect and improve quality of life in patients affected by multifactorial LBP using paravertebral infiltrations[6–9] as well as in LDH using intradiscal infiltrations.[10–17] Its application could be used to prevent or delay surgery in patients who do not respond to conservative treatments. However, to date, there are no randomized controlled trials (RCT) that compare O2O3 versus surgery. The aim of the current RCT was to compare intradiscal O2O3 infiltration vs. oxygen (O2) infiltration vs. surgery.

2. Material and methods

This was a randomized, double-blinded (patients and outcomes assessor) parallel group study aimed to evaluate the effect of O2O3 therapy in the management of patients with lumbar herniated disc requiring surgery according to the criteria of our Department of Neurosurgery. All patients provided informed written consent to participate in the trial, and all procedures conformed to the Declaration of Helsinki of 1975. The clinical trial was approved by the Research Ethics Review Committee of Las Palmas (Spain) and, before the start of the enrollment of patients, it was registered at http://www.clinicaltrials.gov (NCT00566007).

The main objectives of this research were: 1) to evaluate the efficacy of O2O3 infiltration versus O2 infiltration, 2) to evaluate the effectiveness of O2O3 infiltration versus surgery. The secondary objectives were: 1) to evaluate direct hospital costs, 2) to evaluate the safety of the different procedures.

There were three treatment arms: 1) surgery (standard treatment):

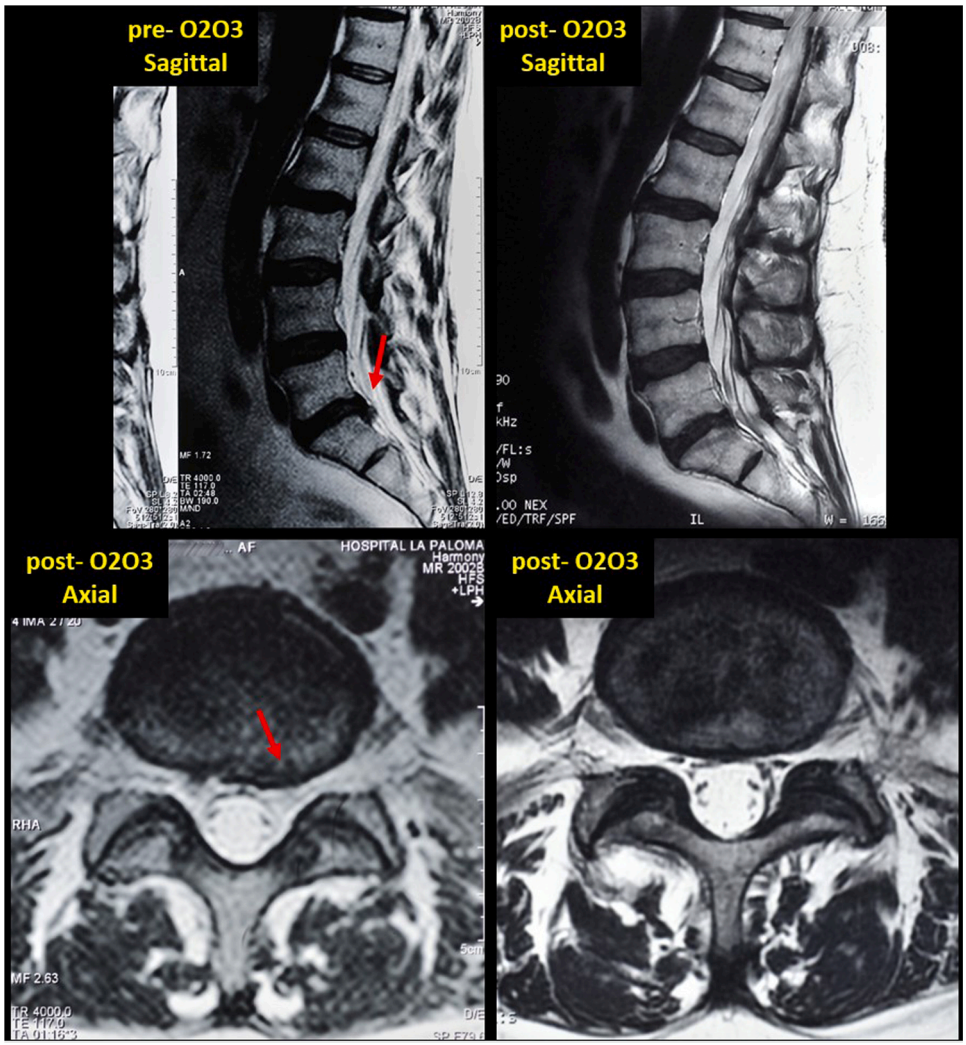

Fig. 2. Images pre- and post- ozone treatment. 59 years old patient on waiting list for surgery because a symptomatic, left paramedial L5-S1 disc herniation (red arrows), with small caudal migration, and S1compression. After randomized, blinded assignment, the patient was treated by intradiscal oxygen-ozone (O2O3) infiltration. Planned surgery was avoided. In the last magnetic resonance images (MRI), nine years after procedure, the patient remained without disc herniation relapse.
Upper Left: Sagittal MRI pre-treatment. *Upper Right:* MRI three years post-treatment. *Lower Left:* Axial MRI pre-treatment. *Lower Right:* Axial MRI three years post-treatment.

discectomy or microdiscectomy; 2) ozone (experimental): intradiscal O2O3 infiltration (concentration: 27 μg/mL (μg O3/mL O2)) + foraminal infiltration of O2O3 + steroids + anesthetic; 3) O2 (sham control): intradiscal O2 infiltration + foraminal infiltration of "O2 + steroids + anesthetic". The neurosurgeons and follow-up physicians were blinded with respect to the infiltration arm.

The main inclusion criteria were the following: patients between 18 and 75 years of age; on waiting list for surgery following diagnosis of herniated disc; sciatic pain ≥ 5 on the visual analog scale (VAS); pain radiated to the appropriate area according to the herniated disc; on the waiting list for disc surgery. The main exclusion criteria were calcified or migrated herniated disc, herniated disc with indications for laminectomy or arthrodesis, clinically relevant partial paralysis, simultaneous cervical and dorsal symptomatic herniated discs, and previous lumbar spine surgery.

Initially, the main variable was pain level assessment according to the VAS. The initial estimated sample size was 156 patients (52 per treatment arm). However, organizational issues beyond our control obliged closure of the study, with only 19 patients having been enrolled between December 2008 and March 2014. Finally, the clinical outcomes were requirements of surgery, safety, and days and costs of hospitalization evaluated five years after treatment of the last recruited patient. Fig. 1 shows the CONSORT diagram.

Statistical analysis included inpatient days and costs from the first treatment plus further surgery if required. Data from the treatment arms are expressed as median (25^{th}–75^{th} percentiles) and were compared using the exact Mann–Whitney *U* test (two-tailed). Values of $P < 0.05$ were considered statistically significant. As a non-inferiority study, the per protocol analysis was considered more relevant; both per protocol and by intention to treat analysis are described in Table 1.

3. Results

The median follow-up was 78 months (26–106). One of the five patients (20 %) initially treated with O2O3 infiltration required subsequent surgery 10 months later. Three of the five patients initially treated with O2 infiltration (60 %) required surgery at the 4^{th}, 6^{th} and 14^{th} months, respectively. One out of the nine patients (11 %) initially treated with surgery required a second surgery eight months later, which was initially declined by the patient, but finally performed 33 months later. No adverse events related with infiltration procedure were observed. Representative images are featured in Fig. 2.

Compared to the surgery arm, patients treated with O2O3 infiltrations required fewer inpatient days: 3 (3–3.5) vs. 0 (0–1.5), $P = 0.012$ and had lower costs: EUR 3702 (EUR 3283–7630) vs. 364 (364–2536), $P = 0.029$. See details in Table 1.

4. Discussion

This report, for the first time in the literature, describes O2O3 infiltration vs. O2 infiltration vs. surgery in patients with disc herniation requiring discectomy or microdiscectomy. In our study, only 20 % of

O2O3 infiltrated patients required further surgery, which is in agreement with the efficacy suggested by previous studies.[10–14] This percentage was clearly lower than the 60 % of O2 infiltrated patients requiring further surgery. Our study agrees with a previous randomized, double-blind clinical trial describing the greater effect of O2O3 infiltration versus O2 infiltration by paravertebral approach.[6] Our study also suggests that the addition of intradiscal O2O3 infiltration leads to better clinical effect than the infiltration of corticosteroid and anesthetic alone, as previously described in another randomized double blind clinical trial.[14] However, whereas the two mentioned clinical trials[6,14] showed results within 6 months of follow-up, our study shows a beneficial effect for up to 5 years after follow-up, with the additional inclusion of a surgery group.

Compared to the surgery group, the O2O3 group required significantly lower number of inpatient days and had lower associated costs. The difference in treatment costs (around EUR 3000 per patient) agrees with the results in a large retrospective study (2589 patients) from Cuba,[18] and could be of additional interest for health services providers.

On the other hand, the beneficial effect of O2O3 in pain has also been reported in knee osteoarthritis RCT[19–21] as well as in different neuropathic pain syndromes in small studies, such as in trigeminal neuralgia,[22] zoster-associated pain,[23] and refractory pelvic pain secondary to cancer treatment.[24,25]

However, the encouraging results described in our work should be interpreted with caution because the study has relevant limitations: first, the very small enrollment and subsequent sample size; second, limitations for completing the initially planned questionnaires of pain and quality of life during follow-up. Both limitations result from structural factors prevalent in our University Hospital at the time and limit the generalizability of the results. Nevertheless, these data could be used as a pilot for larger scale studies. From these results, we have instigated a prospective confirmatory study (NCT03282695), with 80 patients being enrolled in the first 24 months. Results will be available in the middle of 2021.

5. Conclusions

In this very small sample size study, we observed that intradiscal O2O3 infiltrations decreased the requirements for conventional surgery, resulting in a statistically significant decrease in hospitalization and associated costs. These effects and their magnitude are of interest to patients and health services providers. A further validation study is ongoing.

Author statement

Bernardino Clavo: Conceptualization; Data curation; Funding acquisition; Investigation; Methodology; Project administration; Roles/Writing - original draft; Final version review & approval. **Francisco Robaina:** Conceptualization; Investigation; Resources; Supervision; Validation; Final version review & approval. **Gerard Urrutia:** Conceptualization; Methodology; Final version review & approval. **Sara Bisshopp:** Funding acquisition; Investigation; Writing - review & editing; Final version review & approval. **Yolanda Ramallo:** Investigation; Writing - review & editing; Final version review & approval. **Adam Szolna:** Investigation; Final version review & approval. **Miguel A. Caramés:** Investigation; Final version review & approval. **María D. Fiuza:** Conceptualization; Formal analysis; Supervision; Validation; Final version review & approval. **Renata Linertová:** Funding acquisition; Investigation; Writing - review & editing; Final version review & approval

Declaration of Competing Interest

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