Intramuscular paravertebral oxygen-ozone therapy for chronic neck pain and low back pain: evaluation of 6-month clinical outcomes

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Abstract

Spinal pain is recognized as the most common cause of disability, work absenteeism and need of healthcare services worldwide. Although many strategies have been developed for conservative treatment of spinal pain, its increasing prevalence diagnosis highlights the need for new treatments. Oxygen-ozone (O_2–O_3) therapy is considered to be an alternative therapy due to its analgesic and anti-inflammatory effects. This retrospective study evaluated the effects of O_2–O_3 intramuscular paravertebral injections in 76 patients with chronic neck pain or low back pain, in terms of pain and disability reduction, quality of life improvement, and analgesic drug intake. Patients were evaluated before, at the end of the treatment, and at 1, 3 and 6 months after the last treatment, using Numeric Rating Scale, Neck Disability Index or Oswestry Disability Index, and Short Form-12 Health Survey. There were significant beneficial effects of O_2–O_3 therapy in reducing pain and disability reduction and improving quality of life during the 6-month follow-up period. O_2–O_3 therapy was associated with a reduction in analgesic drug intake at each assessment. Our results allow us not only to support treatment with O_2–O_3 intramuscular paravertebral injections as a safe and beneficial treatment for chronic low back pain, but also to consider it as a valuable conservative therapy for patients with chronic neck pain.

Key words: intramuscular ozone; low back pain; neck pain; oxygen-ozone therapy; ozone therapy; ozone; paravertebral injections; paravertebral ozone

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Introduction

Spinal pain is recognized as the most common cause of disability, work absenteeism, and need of healthcare services worldwide.[1] Approximately 70–80% of the population in industrialized countries has experienced low back pain at least once in lifetime,[2] and is estimated that 5.0–10.0% of cases will develop chronic low back pain.[3] Every year, 10–20% of the population experience neck pain for the first time,[4] and about 66% of the population have suffered from cervical pain at least once in their life.[5] Although neck pain is generally believed to have a favorable prognosis, one-third of patients will develop a chronic condition.[6] Numerous strategies have been developed for conservative treatment of spinal pain, such as steroidal and non-steroidal anti-inflammatory treatments, skeletal muscle relaxants, physical therapy, manipulative spinal therapies, acupuncture and mesotherapy.[7,8] However, the increasing prevalence of spinal pain diagnosis highlights the need for new treatment methods.[4,9] Oxygen-ozone (O_2–O_3) therapy is considered a potential therapy through its antioxidant, analgesic, anti-inflammatory and immunomodulating effects.[10] There are multiples routes for therapeutic ozone administration in the treatment of spinal disorders. In paravertebral approach, O_2–O_3 mixture is injected into paraspinal muscles at the level of the herniated disc; whereas in percutaneous intradiscal approach, the gas is injected under radioscopic guidance into the pathologic intersomatic space.[10] In Italy and other Western countries, intramuscular paravertebral injection of O_2–O_3 mixture is the most widely used technique in clinical practice.[11] It has been also defined as "chemical acupuncture" because both the needle and gas injection induce molecular and neurological changes causing pain relief in the majority (70–80%) of patients with low back pain.[10]

In the treatment for low back pain secondary to herniated disc, the level of evidence for long-term pain relief is II-1 for intramuscular O_2–O_3 therapy with 1B strength of recommendation, and II-3 for intradiscal O_2–O_3 therapy with a grade of recommendation 1C.[12] Although O_2–O_3 therapy is widely used common clinical practice in patients with neck pain, a still little evidence support its efficacy.

The aim of this study was the retrospective evaluation of the short-, mid- and long-term clinical effects of intramuscular paravertebral O_2–O_3 therapy in the treatment of patients with chronic neck or low back pain, expressed in terms of pain, disability, quality of life, and drug intake. We hypothesize that O_2–O_3 therapy thank to its antalgic, anti-inflammatory and antioxidant effects, may decrease pain and disability in patients affected by spinal pain, reducing drug intake and improving their quality of life.

Subjects and Methods

Subjects

A total of 105 patients with chronic neck or low back pain were examined in the Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital of Rome ("Sapienza" University of Rome), in the period between March 2017 and June 2018. All patients were subject to clinical assessment, standard X-rays and magnetic resonance imaging (MRI).

Inclusion criteria of this study were: neck or low back pain (with or without radiculopathy) for at least 3 months; intensity of pain > 3 at the numeric rating scale (NRS) in the last week; MRI evidence of discal bulging, disk herniation or spondylarthrosis in the spinal segments involved in the pain.

Exclusion criteria were: severe neurological motor deficit; spinal stenosis; cauda equina syndrome; previous spinal surgery; any contraindication to paravertebral infiltrative therapy with O_2–O_3, such as pregnancy, uncontrolled hyperthyroidism, glucose-6-phosphate dehydrogenase deficiency (favism), severe cardiovascular diseases and heart failure, patent foramen ovale; any condition where spine surgical treatment is recommended. According to the inclusion and exclusion criteria, 76 subjects were eligible, including 51 patients with chronic low back pain and 25 with chronic neck pain.

A total of 29 patients with spinal pain did not meet the eligibility criteria and were excluded from this study. The reasons for patient's ineligibility were as follows: pain lasting less than 3 months (11 patients), NRS intensity pain < 3 (5 patients), glucose-6-phosphate dehydrogenase deficiency (1 patient), uncontrolled hyperthyroidism (2 patients) and pregnant (3 patients). These patients were carried to other conservative treatments. Lastly, three patients showed severe neuromotor deficiency and four patients reported spinal stenosis. This patient group was referred for surgical consultation.

All eligible patients were orally informed about the potential risks of treatment and written informed consent was obtained to treatment interventions. Furthermore, written consent was required from all the subjects to be included in this retrospective study and for data publication. The study was approved by the Institutional Review Board of the University of Rome "Sapienza" (approval No. RS 6482/2021) and was conducted in accordance with good clinical practice and the *Declaration of Helsinki*.

O_2–O_3 therapy

Each patient underwent 12 intramuscular paravertebral injections of O_2–O_3 mixture, with an ozone concentration of 15 µg/mL, obtained by Multiossigen Medical 99 IR generator (Multiossigen S.p.A., Gorle, Bergamo, Italy). The sessions were repeated: 2/week for 2 weeks, then 1/week for 6 consecutive weeks, finally two maintenance sessions at fortnightly intervals for a month.

The intramuscular injection was administered into paraspinal muscles at the level of each vertebral segment affected. In a treatment session were performed two symmetrical injections of 3–5 mL into cervical region, or 10 mL into lumbar region, of O_2–O_3 gaseous mixture, using an extraspinal lateral approach. The most frequently sites treated were those relative to L4–L5 and L5–S1 in lumbar region, and those relative to C5–C6 and C6–C7 in cervical region.

The optimal needle length to perform O_2–O_3 injection was determined by an ultrasound evaluation prior to paravertebral infiltration, as recently described by Latini et al.[13] in 2019. Ultrasonography provides a comprehensive assessment of the region of interest, locating the different landmark structures of the lumbar and cervical spine, using a sagittal and a transverse scan with the patient in the prone or sitting position. Sagittal scanning allows accurate delineation of the intervertebral levels, whereas transverse scanning visualizes the medial paravertebral muscles, site of O_2–O_3 mixture injection. For the needle length selection were performed two linear measurements in transverse plane obtained at 1.5 cm laterally from the spinous process in cervical region (**Figure 1A**), and at 2 cm laterally from the spinous process in lumbar region (**Figure 1B**). The measurement were: (I) the skin-muscle distance, measure between the skin and hyperechoic fascia around the superior border of the muscle; (II) the skin-lamina distance, measure between the skin and the deep border of the muscle adjacent to the hyperechogenic vertebral lamina (**Figure 1**). These two measurements are helpful indicators of the thickness of the paravertebral muscles, allowing the selection of the most appropriate needle length range to perform infiltration into musculature. All ultrasound measurements were performed using a linear-array transducer (Sonoscape P50 Ultrasound scanner, Sonoscape Europe s.r.l.). A 23-gauge spinal needle (length, 30 mm; size, 0.7 mm) or a 22-gauge spinal needle (length, 40 mm; size, 0.7 mm) were most frequently used for lumbar paravertebral injections, instead a 25-gauge spinal needle (length, 16 mm; size, 0.5 mm) or a 25-gauge spinal needle (length, 25 mm; size, 0.5 mm) were tipically used for cervical paravertebral injections.

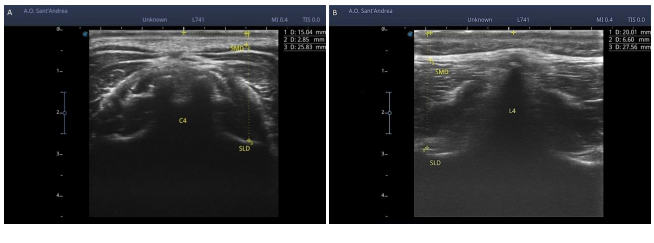

Figure 1: Example of measurements performed in transverse spinous process view.
Note: In transverse view, linear measurements are performed at 1.5 cm laterally from the spinous process in cervical region, and 2 cm laterally from the spinous process in lumbar region (A) At the C4 level, skin-muscle distance (SMD) was 2.85 mm and skin-lamina distance (SLD) was 25.83 mm. (B) At the L4 level, SMD was 6.60 mm and SLD was 27.56 mm. The image was obtained by means of a Sonoscape P50 Ultrasound (Sonoscape Europe s.r.l., Rome, Italy).

Under sterile conditions, medical O_2–O_3 mixture was injected in the paravertebral muscles at 2 cm bilaterally from spinous processes, making sure not inadvertently administer inside a venous/arterial vessel. The O_2–O_3 mixture was introduce slowly avoiding relevant manifestations of pain and promoting homogeneous distribution of the gas through the muscle fibers.

Outcome evaluation

The outcomes were: i) reduction of pain evaluated in all patients with the NRS, ii) reduction of disability evaluated with Neck Disability Index (NDI) or Oswestry Disability Index (ODI), respectively for neck pain or low back pain; iii) improvement of quality of life measured with the Short Form-12 Health Survey (SF-12); and iv) reduction of analgesic drugs intake. All patients were evaluated for the occurrence of adverse effects at the end of treatment and during the 6-month follow-up period.

NRS is the most widely used instrument for pain screening where the patients describe their pain intensity from 0 ("no pain") to 10 ("worst possible pain").[14]

NDI and ODI are the most commonly condition-specific outcome measures used in the management of spinal disorders.[15,16] Both consist in a self-administered questionnaire of 10-item, assessing the level of pain and interference with several physical activities. Each item is rated on a 6-point scale (0–5). The total score is obtained with a sum of the responses and is then expressed as a percentage of the maximum possible score, ranging from 0 (no disability) to 100 (maximum disability).[15,16]

The SF-12 Health Survey is a self-reported 12-item health-related quality-of-life survey. It has demostrated construct validity, good internal consistency reliability and responsiveness in patients with back pain.[17] Two subscales are derived from the SF-12: the Physical Component Summary (PCS-12) score and the Mental Component Summary (MCS-12) score. The evaluation scales were carried out at baseline time (T0), at the end of the treatment (T1), and after 1 (T2), 3 (T3) and 6 (T4) months following the end of the treatment.

Statistical analysis

The descriptive statistics included media with standard deviation for quantitative variables and frequencies and percentages for qualitative variables. To examine the clinical effects of intramuscular paravertebral injections of O_2–O_3 mixture in the treatment of patients with chronic neck pain or low back pain, the paired Student's *t*-test was used. All tests were two-tailed with a significance level of $P < 0.05$. IBM SPSS Statistics ver. 20.0 (IBM SPSS, Chicago, IL, USA) was used for the statistical analyses.

Results

Between March 2017 and June 2018, 105 patients affected by neck pain and low back pain were examined in the Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital of Rome ("Sapienza" University of Rome). As previously reported, 29 patients did not meet the eligibility criteria. Of the 76 eligible subjects, 51 reported chronic low back pain and 25 reported chronic neck pain, as shown in **Figure 2**.

Demographic details and clinical parameters of the participants at baseline (T0) are provided in **Table 1**, respectively for neck pain and low back pain. A high percentage of patients (72% in chronic neck pain group and 62.7% in chronic low back pain group) had received at least one conservative treatment in the past.

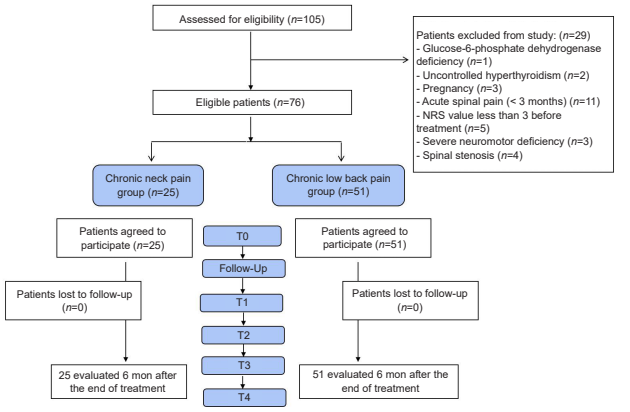

Figure 2: Trial flow chart

Table 1: Demographic and clinical parameters at baseline in patients with chronic neck pain and chronic low back pain

Variables	Chronic neck pain group (n = 25)	Chronic low back pain group (n = 51)
Age (yr)	55.1±9.8	56.1±14.3
Sex		
Male	11 (44)	21 (41.2)
Female	14 (56)	30 (58.8)
Body mass index (kg/m^2)	25.8±4.0	25.3±3.5
Sport		
Yes	10(40)	15 (29.4)
No	15(60)	36 (70.6)
Previous conservative treatments		
Yes	18±72.0	32±62.7
No	7±18.0	19±37.3
Numeric rating scale	6.2±1.8	6.4±2.1
Neck disability index	30.1±14.3	25.6±14.6
Physical component summary score	38.8±6.7	34.3±8.6
Mental component summary score	38.3±11.8	35.8±8.3

Note: Data are expressed as mean ± SD, except for the sex and sport, and were analyzed by paired Student's *t*-test.

Chronic neck pain group

A significant improvement of all outcome measures was observed in patients with chronic neck pain at each assessment (**Table 2**). NRS and NDI were significantly reduced during the follow-up ($P < 0.001$). PCS-12 was significantly improved after treatment (T1 *vs*. T0: $P < 0.001$, T2 *vs*. T0: $P < 0.001$, T3 *vs*. T0: $P = 0.001$, T4 *vs*. T0: $P < 0.001$). MCS-12 was significantly better after treatment (T1 *vs*. T0: $P = 0.013$, T2 *vs*. T0: $P = 0.003$, T3 *vs*. T0: $P = 0.017$, T4 *vs*. T0: $P = 0.005$).

Chronic low back pain group

The clinical results obtained in patients with chronic low back pain are summarized in **Table 2**. NRS, ODI and PCS-12

Table 2: Effect of oxygen-ozone therapy on the pain and disability of patients with chronic neck pain and chronic low back pain

	NRS		NDI		PCS-12		MCS-12	
	Data	*P*-value with T0	Data	*P*-value with T0	Data	*P*-value with T0	Data	*P*-value with T0
Chronic neck pain group (n = 25)								
T0	6.2±±1.8		30.1±14.3		38.8±6.7		38.3±11.8	
T1	3.4±2.1	0	17.4±11.7	0	43.2±6.1	0	41.7±9.9	0.013
T2	3.1±2.1	0	14.9±11.9	0	43.7±5.8	0	42.6±10.2	0.003
T3	3.4±2.4	0	17.5±15.8	0	42.0±6.8	0.001	42.8±11.5	0.017
T4	3.4±2.3	0	16.1±14.5	0	43.2±6.1	0	44.1±10.7	0.005
Chronic low back pain group (n = 51)								
T0	6.4±2.1		25.6±14.6		34.3±8.6		35.8±8.3	
T1	3.3±1.9	0	15.4±13.2	0	40.6±7.8	0	38.7±9.7	0.266
T2	2.8±2.2	0	11.7±12.6	0	43.1±7.4	0	42.0±10.2	0
T3	2.7±2.2	0	11.4±12.4	0	43.3±7.6	0	42.7±9.9	0
T4	3.2±2.6	0	13.3±13.7	0	42.8±8.3	0	41.8±10.2	0

Note: Data are expressed as mean ± SD and were analyzed by paired Student's *t*-test. MCS-12: Mental component summary score; NRS: numeric rating scale; ODI: Oswestry disability index; PCS-12: physical component summary score; T0: baseline time; T1: at the end of the treatment; T2–4: after 1, 3 and 6 months following the end of the treatment.

were significantly reduced during the follow-up ($P < 0.001$). MCS-12 was not significantly better at the end of the treatment (T1 *vs*. T0: $P = 0.266$), whereas was significantly better after treatment (T2 *vs*. T0: $P < 0.001$, T3 *vs*. T0: $P < 0.001$, T4 *vs*. T0: $P < 0.001$). In both groups of patients clinical outcome were considerably improved at the end of the treatment, and this improvement was persistent at 1-, 3- and 6-month follow-up time.

Furthermore, intramuscular paravertebral O_2–O_3 therapy was followed by a reduction of analgesic drug intake in both groups of patients at each assessment (**Table 3**). No clinically relevant side effects were reported during and after the treatment.

Table 3: Intake of oral drugs in chronic neck pain and chronic low back pain patients undergoing oxygen-ozone therapy

	Intake	Non-intake
Chronic neck pain group (n = 25)		
T0	10 (40.0)	15 (60.0)
T1	2 (8.0)	23 (92.0)
T2	1 (4.0)	24 (96.0)
T3	2 (8.0)	23 (92.0)
T4	3 (12.0)	22 (88.0)
Chronic low back pain group (n = 51)		
T0	22 (43.1)	29 (56.9%)
T1	7 (13.7)	44 (86.3)
T2	7 (13.7)	44 (86.3)
T3	10 (19.6)	41 (80.4)
T4	13 (25.5)	38 (74.5)

Note: Data are expressed as number (percent) and were analyzed by paired Student's *t*-test. T0: baseline time; T1: at the end of the treatment; T2–4: after 1, 3 and 6 months following the end of the treatment.

Discussion

Results analysis of this retrospective study shows significant beneficial effects of intramuscular paravertebral injections of O_2–O_3 mixture on spinal pain, disability and drug intake reduction and quality of life improvement during the 6-month follow-up period.

Few research studies[12,18-20] and a review article[11] evaluated the effects of O_2–O_3 intramuscular lumbar paravertebral injections in the management of low back pain secondary to herniated disc. In this context, a randomized prospective study[18] compared the therapeutic efficacy of epidural steroid injections and paravertebral infiltration of O_2–O_3 gas mixture in the treatment of patients with acute or chronic irradiating low back pain caused by herniated disc, showing a higher success rate for O_2–O_3 infiltration in short and long-term remission of pain. Other randomized controlled studies[12,19] evaluated the effectiveness of lumbar paravertebral injections of O_2–O_3 in patients with lumbar radiculopathies caused by disc herniation, comparing the application of ozone with other treatments or simulated therapy. If compared with a pharmacological therapy based on non-steroidal anti-inflammatory drug,[19] O_2–O_3 therapy showed a 80% success rate *versus* 50% for the anti-inflammatory analgesic drug group; if compared with a sham procedure,[12] patients treated with ozone had significantly lower pain scores compared to patients treated with simulated therapy (61% *vs*. 33%). More recently, an observational retrospective study[20] evaluated the effects of intramuscular O_2–O_3 infiltration in patients with chronic back pain associated with disc herniation, in comparison with global postural re-education and with a combination of both O_2–O_3 + global postural re-education. Ozone therapy seems to be associated with the best short-term effects on pain, and these could be maintained by the long-lasting action of global postural re-education.

O_2–O_3 therapy is widely used common clinical practice in patients with cervical pain, although a still little evidence support its efficacy. We found few studies in the literature of patients with neck pain treated using paravertebral ozone injections. In 2020, a case series study evaluated the effects of 12 cervical intramuscular paravertebral injections of O_2–O_3 (5 mL with 16 μg/mL ozone) in 168 patients affected by radicular neck pain.[21] The participants showed a significant pain reduction ($P < 0.001$) within 1–5 years of follow-up.

In the same way, Ucar et al.[22] in a retrospective study assessed the role of O_2–O_3 paravertebral injection in 72 patients with neck pain due to cervical disc diseases. Patients received 30 mL of 20 μg/mL O_2–O_3 gas into the paravertebral space, once a week for 6 weeks, showing a significant improvement in visual analog scale and Japanese Orthopedic Association scores at both 2 and 6 months.

This retrospective study shows positive effects of O_2–O_3 intramuscular paravertebral injections in the treatment of spinal pain associated with discal bulging, disk herniation or spondylarthrosis in patient suffering from chronic neck pain or low back pain.

In both groups of patients, pain and disability is significantly decreased at the end of treatment and during the 6-month follow-up period. Data show that clinical pain and disability outcomes (measured by NRS, NDI or ODI) are considerably decreased at the end of the treatment, and this reduction is persistent at 1-, 3-, and 6-month follow-up time points. Thanks to the pain and disability reduction obtained, perceived quality of life appears to be improved in both patient groups. Furthermore, intramuscular paravertebral O_2–O_3 therapy is followed by a reduction of analgesic drug intake in both groups at every assessment, emphasizing the antalgic and anti-inflammatory effect of O_2–O_3 therapy. Our findings are in agreement with those of other authors who showed a significantly lower number of days on nonsteroidal anti-inflammatory drugs after ozone therapy.[12] From this point of view, intramuscular paravertebral injection of O_2–O_3 mixture may act as a local antiphlogistic therapy.

The benefits obtained from O_2–O_3 therapy are visible during and/or immediately after the end of treatment, and are maintained over time, suggesting O_2–O_3 therapy may lead to persistent changes in the microenvironment, normalizing the cellular redox balance, resolving inflammation and recovering homeostatic state.

In addition, clinical effects obtained in patients group suffering from chronic low back pain in terms of pain reduction, disability, and drug consumption, are comparable to those observed in patients group with chronic neck pain at the end of treatment and during the 6-month follow-up period. This is probably because low back pain and neck pain share the similar pathogenic mechanisms, resulting both responsive to O_2–O_3 therapy.

There are many literatures discussing the beneficial effects of the oxygen and ozone therapy on different pathophysiological process.[11,23,24] Probable mechanism of action of the O_2–O_3 therapy may be based on the chemical properties of O_3, an unstable allotropic form of oxygen, which shows an antalgic, anti-inflammatory, antioxidant effects and an immunomodulatory action.[25,26] These are performed by: (i) influencing the cellular metabolism, (ii) modulating pro-inflammatory cytokine response and increasing release of antagonistic molecules, such as analgesic compounds and immunosuppressor cytokines, (iii) restoring redox balance through the synthesis of endogenous antioxidant enzymes (glutathione peroxidase, superoxide dismutase and catalase) and, in addition, (iv) regulation of peripheral tissue oxygenation through vasodilatation and angiogenic response.[23,25] In particular, the efficacy of the O_2–O_3 therapy could be related to the controlled, moderate, and transient oxidative stress produced by the reactions of O_3 with the biological tissues. Through a number of second messenger in various intracellular signaling pathways it induces the activation of nuclear transcriptional factors able to stimulate an adaptive antioxidant response, as nuclear factor erythroid 2-related factor 2, and upregulation of the antioxidant enzymes, such as catalase, superoxide dismutase, GSH-peroxidase.[27] This mechanism is the basis of the paradoxical phenomenon for which a strong oxidizing molecule can determinate, on the contrary, an antioxidant reaction.[27]

O_2–O_3 therapy appears to have few or no adverse effects when used at the appropriate therapeutic concentrations.[28,29] The adverse effects of O_2–O_3 therapy can be distinguished in effects based on the O_2–O_3 mixture (feeling of heaviness or burning at the injection until a vagal crisis), and those based on the administration technique (hematoma, pain and infection due to a non-aseptic condition). However, patient adverse events are rare and can be reduced with good procedures.[30] In our series, O_2–O_3 therapy was well-tolerated and no clinically relevant side effects were recorded during the treatment and in the 6-month follow-up period.

The main limitations of this study are the retrospective nature and the small number of patients in chronic neck pain group. Moreover, the lack of a control group does not allow us to compare the results with other conservative treatments. Although the retrospective design of the study, our results allow us not only to support treatment with O_2–O_3 intramuscular paravertebral injections as a safe and beneficial treatment for chronic low back pain (as previously confirmed by literature), but also to consider it as a valuable conservative treatment for chronic neck pain. The current study provides preliminary data and leads to the development of future prospective studies.

Furthermore, the non-invasive ultrasound method used in this study provides accurate measurements of the paravertebral muscles depth and of the subcutaneous tissue thickness, allowing selecting the most suitable needle length to perform infiltration. It is helpful for patients with specific adipose tissue distribution, where the length of the needle normally used for O_2–O_3 injections is not long enough to reach the paraspinal muscles, thus improving accuracy and safety of the treatment.

Author contributions
Study design, concept and definition: EL, SMN, ERC, DB, FS, DT, MV, MCV. All authors read and approved the final version of the paper for publication.
Conflicts of interest
None.
Data availability statement
No additional data are available.

References

1. Rubin DI. Epidemiology and risk factors for spine pain. *Neurol Clin*. 2007;25:353-371.
2. Andersson GB. Epidemiological features of chronic low-back pain. *Lancet*. 1999;354:581-585.
3. Liao ZT, Pan YF, Huang JL, et al. An epidemiological survey of low back pain and axial spondyloarthritis in a Chinese Han population. *Scand J Rheumatol*. 2009;38:455-459.
4. Hoy DG, Protani M, De R, Buchbinder R. The epidemiology of neck pain. *Best Pract Res Clin Rheumatol.* 2010;24:783-792.
5. Binder A. The diagnosis and treatment of nonspecific neck pain and whiplash. *Eura Medicophys*. 2007;43:79-89.
6. Côté P, Cassidy DJ, Carroll LJ, Kristman V. The annual incidence and course of neck pain in the general population: a population-based cohort study. *Pain*. 2004;112:267-273.
7. Hooten WM, Cohen SP. Evaluation and treatment of low back pain: a clinically focused review for primary care specialists. *Mayo Clin Proc*. 2015;90:1699-1718.
8. Cohen SP, Hooten WM. Advances in the diagnosis and management of neck pain. *BMJ*. 2017;358:j3221.
9. Hoy D, Brooks P, Blyth F, Buchbinder R. The Epidemiology of low back pain. *Best Pract Res Clin Rheumatol.* 2010;24:769-781.
10. Bocci V, Borrelli E, Zanardi I, Travagli V. The usefulness of ozone treatment in spinal pain. Drug Des Devel Ther. 2015;9:2677-2685.
11. Paoloni M, Di Sante L, Cacchio A, et al. 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. *Spine (Phila Pa 1976)*. 2009;34:1337-1344.
12. Magalhaes FN, Dotta L, Sasse A, Teixera MJ, Fonoff ET. Ozone therapy as a treatment for low back pain secondary to herniated disc: a systematic review and meta-analysis of randomized controlled trials. *Pain Physician*. 2012;15:E115-129.
13. Latini E, Curci ER, Massimiani A, et al. Ultrasonography for oxygen-ozone therapy in musculoskeletal diseases. *Med Gas Res*. 2019;9:18-23.
14. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. *J Gen Intern Med.* 2007;22:1453-1458.
15. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa 1976)*. 2000;25:2940-2952; discussion 2952.
16. Vernon H, Mior S. The Neck Disability Index: a study of reliability and validity. *J Manipulative Physiol Ther*. 1991;14:409-415.
17. Luo X, George ML, Kakouras I, et al. Reliability, validity, and responsiveness of the short form 12-item survey (SF-12) in patients with back pain. *Spine (Phila Pa 1976)*. 2003;28:1739-1745.
18. Yang S, Kim W, Kong HH, Do KH, Choi KH. Epidural steroid injection versus conservative treatment for patients with lumbosacral radicular pain: A meta-analysis of randomized controlled trials. *Medicine*. 2020;99:e21283.
19. Melchionda D, Milillo P, Manente G, Stoppino L, Macarini L. Treatment of radiculopathies: a study of efficacy and tollerability of paravertebral oxygen-ozone injections compared with pharmacological anti-inflammatory treatment. *J Biol Regul Homeost Agents*. 2012;26:467-474.
20. Apuzzo D, Giotti C, Pasqualetti P, Ferrazza P, Soldati P, Zucco GM. An observational retrospective/horizontal study to compare oxygen-ozone therapy and/or global postural re-education in complicated chronic low back pain. *Funct Neurol*. 2014;29:31-39.
21. Martinelli M, Giovannangeli F, Venditto T, Travagli V. The use of oxygen ozone therapy in the treatment of cervicobrachial pain: case series study. *J Biol Regul Homeost Agents*. 2020;34:47-55. Special issue: Ozone therapy.
22. Ucar D, Uçar S, Özcan Ç, Polat Ö, Çaçan MA, Uçar BY. Retrospective observational study of intramuscular oxygen-ozone therapy for the treatment of neck pain: cervical paravertebral injection. *Med Gas Res.* 2020;10:170-173.
23. Molinari F, Rimini D, Liboni W, et al. Cerebrovascular pattern improved by ozone autohemotherapy: an entropy-based study on multiple sclerosis patients. *Med Biol Eng Comput.* 2017;55:1163-1175.
24. Bocci V, Zanardia I, Valacchi G, Borrelli E, Travagli V. Validity of oxygen-ozone therapy as integrated medication form in chronic inflammatory diseases. *Cardiovasc Hematol Disord Drug Targets*. 2015;15:127-138.
25. Bocci V, Luzzi E, Corradeschi F, Paulesu L, Di Stefano A. Studies on the biological effects of ozone: 3. An attempt to define conditions for optimal induction of cytokines. *Lymphokine Cytokine Res*. 1993;12:121-126.
26. Richelmi P, Valdenassi L, Bertè F. Pharmacological principles underlying oxygen-ozone therapy. *Neuroradiol J.* 2001;14:17-22.
27. Valdenassi L, Franzini M, Simonetti V, Ricevuti G. Oxygen-ozone therapy: paradoxical stimulation of ozone. *Ozone Ther.* 2016;1:2-4.
28. Bocci VA. Scientific and medical aspects of ozone therapy. State of the art. *Arch Med Res*. 2006;37:425-435.
29. Steppan J, Meaders T, Muto M, Murphy KJ. A metaanalysis of the effectiveness and safety of ozone treatments for herniated lumbar discs. *J Vasc Interv Radiol*. 2010;21:534-548.
30. Perri M, Grattacaso G, di Tunno V, et al. T2 shine-through phenomena in diffusion-weighted MR imaging of lumbar discs after oxygen-ozone discolysis: a randomized, double-blind trial with steroid and O_2–O_3 discolysis versus steroid only. *Radiol Med.* 2015;120:941-950.

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