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Clinical Study

Intradiscal oxygen-ozone chemonucleolysis versus microdiscectomy for lumbar disc herniation radiculopathy: a non–inferiority randomized control trial

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Abstract

BACKGROUND CONTEXT: Low back pain with or without radicular leg pain is an extremely common health condition significantly impacting patient's activities and quality of life. When conservative management fails, epidural injections providing only temporary relief, are frequently utilized. Intradiscal oxygen-ozone may offer an alternative to epidural injections and further reduce the need for microdiscectomy.

PURPOSE: To compare the non–inferiority treatment status and clinical outcomes of intradiscal oxygen-ozone with microdiscectomy in patients with refractory radicular leg pain due to single-level contained lumbar disc herniations.

STUDY DESIGN / SETTING: Multicenter pilot prospective non–inferiority blocked randomized control trial conducted in three European hospital spine centers.

PATIENT SAMPLE: Forty-nine patients (mean 40 years of age, 17 females/32 males) with a single-level contained lumbar disc herniation, radicular leg pain for more than six weeks, and resistant to medical management were randomized, 25 to intradiscal oxygen-ozone and 24 to microdiscectomy. 88% (43 of 49) received their assigned treatment and constituted the AS-Treated (AT) population.

OUTCOME MEASURES: Primary outcome was overall 6-month improvement over baseline in leg pain. Other validated clinical outcomes, including back numerical rating pain scores (NRS), Roland Morris Disability Index (RMDI) and EQ-5D, were collected at baseline, 1 week, 1-, 3-, and 6-months. Procedural technical outcomes were recorded and adverse events were evaluated at all follow-up intervals.

METHODS: Oxygen-ozone treatment performed as outpatient day surgeries, included a one-time intradiscal injection delivered at a concentration of 35±3 μg/cc of oxygen-ozone by a calibrated delivery system. Discectomies performed as open microdiscectomy inpatient surgeries, were without spinal instrumentation, and not as subtotal microdiscectomies. Primary analyses with a non

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−inferiority margin of -1.94-point difference in 6-month cumulative weighted mean leg pain NRS scores were conducted using As-Treated (AT) and Intent-to-Treat (ITT) populations. In post hoc analyses, differences between treatment groups in improvement over baseline were compared at each follow-up visit, using baseline leg pain as a covariate.

RESULTS: In the primary analysis, the overall 6-month difference between treatment groups in leg pain improvement using the AT population was -0.31 (SE, 0.84) points in favor of microdiscectomy and using the ITT population, the difference was 0.32 (SE, 0.88) points in favor of oxygen-ozone. The difference between oxygen-ozone and microdiscectomy did not exceed the non−inferiority 95% confidence lower limit of treatment difference in either the AT (95% lower limit, -1.72) or ITT (95% lower limit, -1.13) populations. Both treatments resulted in rapid and statistically significant improvements over baseline in leg pain, back pain, RMDI, and EQ-5D that persisted in follow-up. Between group differences were not significant for any outcomes. During 6-month follow-up, 71% (17 of 24) of patients receiving oxygen-ozone, avoided microdiscectomy. The mean procedure time for oxygen-ozone was significantly faster than microdiscectomy by 58 minutes ($p<.0010$) and the mean discharge time from procedure was significantly shorter for the oxygen-ozone procedure (4.3±2.9 hours vs. 44.2±29.9 hours, $p<.001$). No major adverse events occurred in either treatment group.

CONCLUSIONS: Intradiscal oxygen-ozone chemonucleolysis for single-level lumbar disc herniations unresponsive to medical management, met the non−inferiority criteria to microdiscectomy on 6-month mean leg pain improvement. Both treatment groups achieved similar rapid significant clinical improvements that persisted and overall, 71% undergoing intradiscal oxygen-ozone were able to avoid surgery.

Keywords: Chemonucleolysis; Leg pain; Lumbar disc herniation; Microdiscectomy; Non−inferiority RCT; Intradiscal oxygen-ozone; Radiculopathy

Introduction

Low back pain with or without leg pain is an extremely common health condition globally with highly variable annual prevalence rates of 1.0%−58.1% [1−4]. Back pain also has a significant impact on the healthcare system [5] and is one of the most common causes for seeking medical care [1]. Disc herniation has been defined as the "localized displacement of nucleus, cartilage, fragmented apophyseal bone or fragmented annular tissue beyond the intervertebral disc space" [6]. Herniated spinal discs are the most frequent reason for visits to an orthopedic or neurosurgeon and fifth most common cause of hospitalization [7]. Due to the high incidence of symptomatic disc herniation [8,9], discectomy is also one of the most common surgical procedure performed by spine surgeons [10,11].

The standard of practice for first line treatment is a minimum 4−6 weeks of conservative management for patients with low back pain, and for those with chief complaints of radiating leg pain as a result of a primary lumbar disc herniation [12−14]. A distinction between patient groups having back pain and those having leg pain associated with their back pain, is important because there are several prognostic differences. Those with radiating leg pain have significantly more pain and disability than those with back pain alone at baseline and at follow-up [15,16]. They are also more likely to require more healthcare resources [17,18] and experience less favorable outcomes [19−21].

For patients with herniated disc radiculopathy whose pain is unmanaged with conservative therapies, a range of minimally invasive interventions is intended as an intermediate step between conservative management and various surgical options. Percutaneous therapies can include injections with various corticosteroids and analgesics or decompressive therapies achieved either by mechanical, thermal or chemical techniques [22].

Epidural steroid injection (ESI) is a commonly and increasingly used procedure to treat local inflammatory processes associated with lumbar disc herniation [23]. Dramatic increases in utilization of ESIs have been reported in the US Medicare population with rates increasing from 309 to 2,149 per 100,000 between 2000 and 2009, representing an annual growth rate of 24% [24,25]. The effectiveness of ESIs have been assessed in multiple systematic reviews [23,26−30]. Four of them specifically considered sciatica or lumbar disc herniations [23,27,29,30]. The reviews generally reported that improvements in leg pain were of limited clinical benefit, often requiring multiple injections, and more likely to be experienced only immediately or in the short-term within 3 months. Another review [31] focusing on studies reporting the surgery-sparing effects of ESI for spinal pain, concluded that ESIs compared to controls, were not surgery sparing in the short- or -longer term.

Oxygen-ozone treatment of painful spinal conditions was first proposed in the 1980s [32] as a treatment for lumbar disc herniation, and since then, has been reported in multiple clinical cohort studies [33−38]. Several mechanisms have been postulated to explain the causes of pain associated with intervertebral herniated discs, as well as the mechanism of action of oxygen-ozone injections on these processes [39−42]. Symptoms of disc herniations are

thought to be caused by direct mechanical compression of the nerve root or nerve root ganglion and an indirect compression on perineural structures. After this injury, a complex interaction of biochemical, neural and inflammatory processes results in the epidural environment of peripheral nerve roots and the ganglia surrounding intervertebral discs.

Oxygen-ozone injections for intervertebral disc herniations, particularly intradiscal injections, produce their main treatment effect of disc volume reduction or shrinkage of the nucleus pulposus through dehydration, and chemonucleolysis which reduces compression on nerve roots [43]. The therapeutic goal of intradiscal oxygen-ozone injections to reduce disc volume, has been documented in several prospective imaging investigations of lumbar disc herniation [44−48]. Magnetic resonance imaging (MRI) investigations have also documented reductions in disc volume that were significantly greater after oxygen-ozone injections than they were after steroid injections [43,44,47,49]. Oxygen-ozone also has anti−inflammatory properties and when also injected into the periganglionic region has been shown to be useful for reducing inflammation by modulating inflammatory cytokines and prostaglandins [39,41,50].

The clinical effectiveness of intradiscal oxygen-ozone injections for lumbar disc radiculopathy has also been compared to epidural steroid and anesthetic injections in several randomized control trials (RCT) [34,39,47,51,52] and was shown to be more effective than these injections [34,47]. Although there has been one prospective matched cohort study [53] comparing intradiscal oxygen-ozone to microdiscectomy for lumbar disc herniation, to our knowledge, there has not been a RCT comparing these two **t**reatments for lumbar disc herniation. The purpose of this multicenter RCT was to compare the non−inferiority treatment status of intradiscal oxygen-ozone compared to microdiscectomy for single-level lumbar disc herniation radicular leg pain refractory to conservative management.

Materials and methods

Three European hospital sites participated in this multicenter pilot RCT. Interventional neuroradiologists performed the intradiscal oxygen-ozone procedures and spine surgeons performed the microdiscectomies. All participating operators had more than 10 years of spine experience. A neurosurgeon with experience in the use of oxygen-ozone served as the medical monitor (JB). Training was provided by the medical monitor and corporate device sponsor to ensure uniformity. Oxygen-ozone consoles and cartridges were provided by the sponsor. All sites received approval from their local Ethical Committee and all subjects provided written informed consent. The study was independently monitored by a clinical research organization in accordance with Good Clinical Practice and listed on clinicaltrials.gov under identifier NCT02525120. The Consolidated Standards of Reporting Trials (Consort) [54] checklist for reporting this RCT is available in Additional File 1, included in the appendix.

Table 1
Summary of inclusion and/or exclusion criteria

Inclusion criteria
1. Single-level disc herniation.
2. At least 50% of the disc height of the normal adjacent disc and/or s.
3. Signal intensity of the herniated disc was equal or greater than the rest of the nucleus pulposus.
4. A dermatomal distribution of pain consistent with their radiographic findings.
5. Leg pain greater than or equal to 5 of 10 on the NRS.
6. Symptoms lasting for at least 6 wk.
7. Aged 18−65 y old.
8. BMI<40.

Exclusion Criteria
1. Disc herniation extending past the facet joint.
2. Presence of a non−contiguous disc fragment.
3. Impairment of bladder and/or bowel function or motor impairment in the affected leg.
4. An epidural steroid injection in the past two wk.
5. Previous discectomy, arthroplasty, or fusion at any lumbar level.
6. Symptomatic lumbar stenosis.
7. Symptomatic sacroiliac joint.
8. Symptomatic foraminal stenosis due to severe degenerative disease.
9. History of spinal tumor, fracture, or infection.
10. Active infection.
11. Females of childbearing age that are known to be pregnant or wishing to become pregnant during the study.
12. Fibromyalgia.
13. Pending litigation against a healthcare provider.
14. More than 3 mo of continuous sick leave prior to enrollment.
15. Known drug or alcohol abuse.
16. Diagnosed psychiatric disease or psychological distress.
17. Known to be affected by favism (G6PD deficiency).

The study inclusion and/or exclusion criteria are provided in Table 1**.** Eligible patients were between 18 and 65 years, with leg pain intensity NRS $\geq$ 5.0, and symptoms lasting at least 6 weeks. Lumbar disc herniations were single-level, having nerve root compression, and retaining at least 50% of adjacent disc height. Patients with herniations involving non−contiguous disc fragments, extending past the facet joint, or recurrence were excluded. Those having any prior spinal surgeries or epidural steroid injections in the past two weeks were also excluded. Disc herniation was confirmed on pre-operative MRI examinations by experienced neuroradiologists. Clinical findings of a dermatomal distribution of pain consistent with radiographic findings were also required. Subjects were randomized in a 1:1 ratio to either oxygen-ozone intradiscal injection or microdiscectomy groups. Randomization procedures involved a block design stratified by center using a computerized random number generator allocation sequence. Randomization lists were prepared by the trial's statistician (DH) and the randomization schedule was unknown to treating physicians and allocation of assignments were only provided to them after their randomization request. The two procedures were

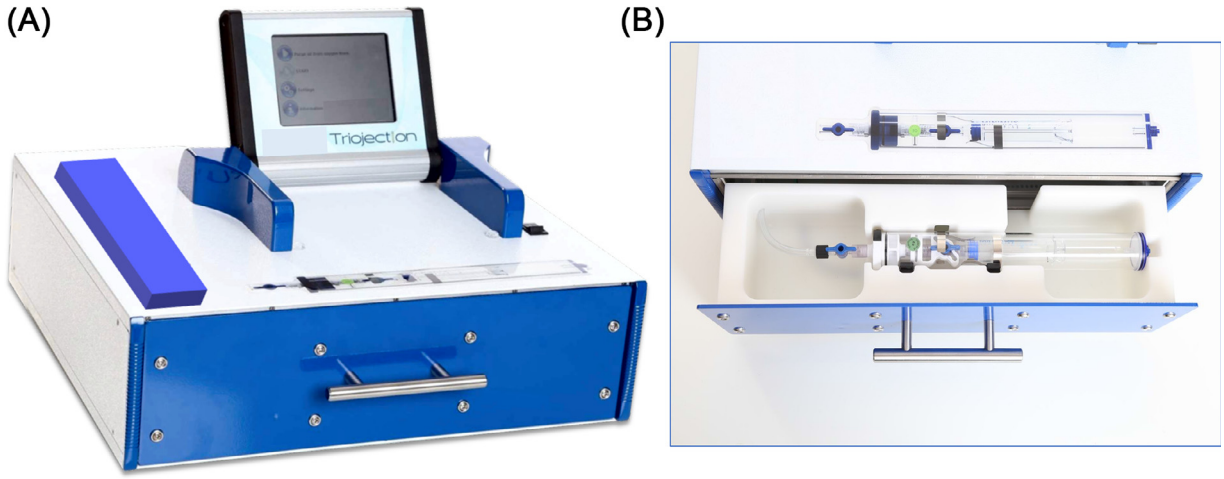

Fig. 1. The oxygen-ozone system. (A) The sterile syringe cartridge. (B) the console with a syringe cartridge in place.

performed by different specialties in different operative setting so it was not possible to blind the interventionalists or the patients to treatments. Outcome assessors were blind to the treatment arm assignment of patients.

The gas mixture is created in the angio suite by an oxygen-ozone generator system (Minimus Triojection now owned by Spinafx Medical, Toronto Ontario, Canada) consisting of a sterile syringe cartridge and a console that accurately measures oxygen-ozone within a pre-sterilized syringe (Fig. 1). The system produces 14 mL of oxygen-ozone gas at a standardized concentration of 35±3 micrograms (levels visible on the console LCD display) within 3 minutes and holds the concentration fixed for up to 60 minutes. The design of a sterile syringe cartridge and a gas filter integrated into the syringe cartridge ensures gas inside the syringe is not contaminated. Oxygen is converted to ozone directly in the syringe, eliminating the risk of dilution or contamination with a transfer from a non−sterile ozone generator to a sterile syringe. The concentration of ozone is measured inside the syringe using an ultraviolet photometer. The syringe gaskets are made of oxygen-ozone resistant materials, and the syringe lubricated with silicone mist, preventing oxygen-ozone degradation or reaction byproducts, and these features minimize the ability of the ozone to react with its surroundings.

Intradiscal oxygen-ozone injections were performed with patients under conscious sedation with sterile technique and local anesthesia. Prophylactic antibiotics were administered within 30−60 minutes of the procedure commencing. A 15 cm 22 g needle was inserted from a paravertebral oblique approach or a posterolateral extra-articular approach through Kambin's triangle into the center of the herniated disc, using fluoroscopic imaging guidance to confirm needle placement (Fig. 2). The entire 14 mL oxygen-ozone gas was injected into the disc, when possible, and gas was allowed to flow through the herniation and into the epidural space adjacent to the nerve root. The time required to administer the injection and the approximate amount of gas injected into the disc and foraminal space was registered by the practitioner. A single procedure was performed and other concurrent injections of steroid or anesthetic were not administered during the primary procedure. All procedures were performed as outpatients in a same day surgery regimen. Patients were discharged with instructions to return to normal activities after 5−7 days, with specific instruction for avoiding bending, and weight lifting for the first 2 weeks. Pain medications were not prescribed on discharge.

Conventional open microdiscectomy under microscopic visualization was performed in the trial by surgeons according to the Caspar microsurgical approach [55]. Subtotal microdiscectomy (removal of the entire pulposus) was not intended and removal of bony lamina or medial portion of facet joint was minimal when deemed necessary. No instrumentation was applied to the spine. Prophylactic antibiotics were administered within 30−60 minutes of the procedure commencing and surgeries were performed under general anesthesia.

The amount of disc material removed, blood loss, and length of incision were estimated after surgery. Patients operated early in the morning were allowed to mobilize later in the afternoon and discharged as per usual care at participating hospitals. Patients were discharged with analgesia and anti−inflammatory prescriptions when deemed necessary. For both procedures, time in the operating room, and time from the end of procedure to discharge were recorded.

Subjects were evaluated at baseline, 1 week, 1-, 3- and 6 months. Follow-up was conducted by independent clinical research organizations. The primary outcome of leg pain improvement assessed as 0−10-point Numerical Rating Scale (NRS), was based on all visits up to, and including 6 months. Other clinical outcome measures included separate NRS scores for back pain, Roland Morris Disability Index (RMDI) [56], and the EQ-5D quality of life questionnaire [57]. Baseline MRI documentation of radiographic parameters included nerve root compression, herniation lumbar

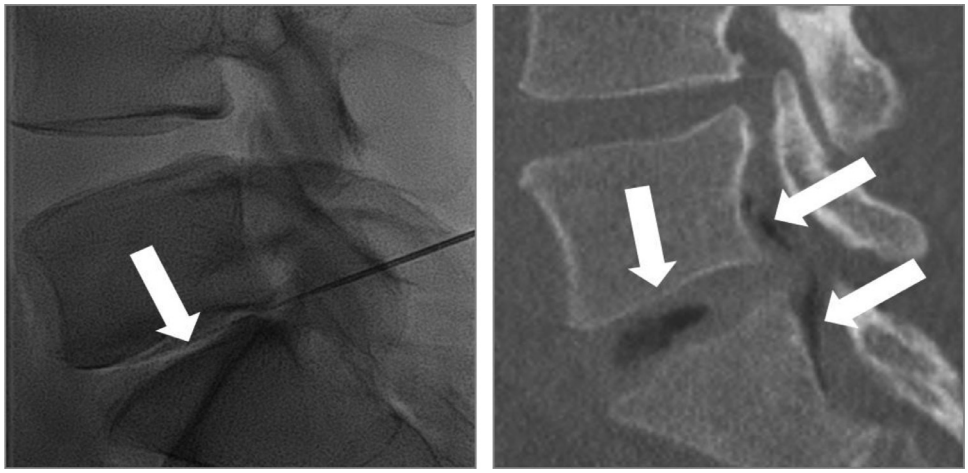

Fig. 2. Intraoperative fluoroscopic images showing placement of the spinal needle and post-operative CT imaging shows gas has been injected into the nucleus pulposus with some spread to the anterior epidural space via an annular tear.

level, side of herniation, disc height and disc signal intensity. The results of the follow-up MRI investigations, scheduled for all patients to evaluate evidence of disc degeneration at the index and adjacent levels, are the subject of a separate report. Adverse events were collected at all follow-up visits and those being monitored after oxygen-ozone injections included: infections, nerve damage, light headiness, headache, arachnoiditis, hematoma, seizures, bowel or bladder dysfunction, bleeding, and transient blindness. Adverse events being monitored following microdiscectomy included: infection, epidural scarring, nerve injury, dural tear, reherniation or disc collapse, and excessive blood loss.

The study was a non–inferiority RCT with the predefined primary endpoint as improvement in leg pain NRS scores over six months (Fig. 3). An analysis of covariance (ANCOVA), adjusted using baseline leg pain, was used to determine the mean, and standard error of the difference between treatments. Post hoc analysis comparing differences between treatment groups in leg pain improvement over baseline were made at each follow-up point. Summary statistics were calculated for all outcome measures.

A non–inferiority margin of -1.94 points chosen to preserve at least half of the 3.88 point expected mean benefit of microdiscectomy for leg pain, was derived from pooled results of several trials [58–60]. Non–inferiority status, evaluated by the fixed-margin method, was met if the lower limit of the one-sided 95% confidence interval for 6-month differences in mean leg pain scores did not exceed the 1.94 non–inferiority margin. The primary analysis was done using an As-Treated (AT) analysis (including all subjects receiving the assigned treatment) and then repeated using

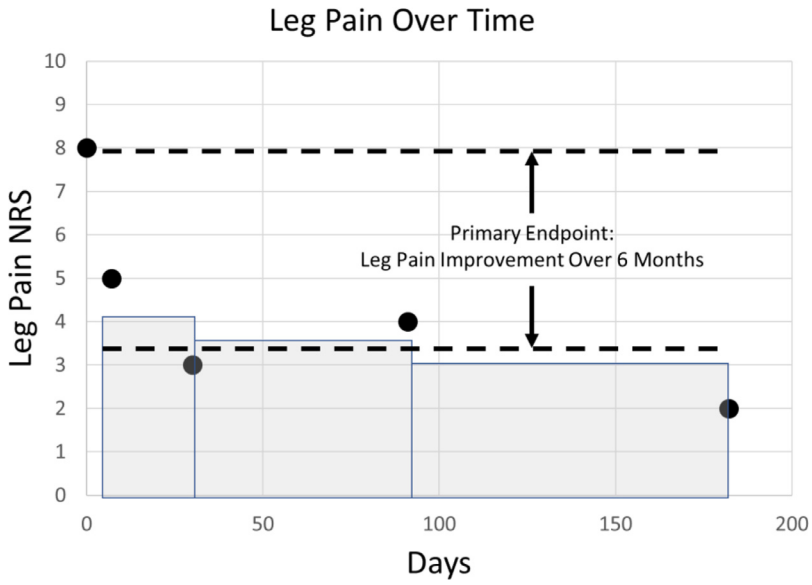

Fig. 3. Construction of the primary clinical endpoint. The primary endpoint is the average leg pain over the course of six months. Circles show the representative pain scores recorded at baseline, 1 week, 1-, 3-, and 6 months. Baseline leg pain was used as a covariate to estimate the improvement.

an Intent-To-Treat (ITT) analysis (all subjects assigned to randomization). For subjects dropping out after randomization, the last value was carried forward. Crossovers to microdiscectomy were allowed after 1 month and decisions were made jointly by the patient and the physician. For missed visits, the previous value was substituted.

The study sample size was based on studies involving microdiscectomy for lumbar disc herniation radiculopathy with similar indications and endpoints (as above). An expected mean 6-month improvement in leg pain was 3.88 points with a standard deviation of 2.6 points. With these assumptions, p=.05 and a power of 80%, and a one-sided 95% confidence limit to assess non−inferiority, the desired sample size was 23 subjects per group. The expected drop-out rate over the first 6 months was estimated at 10%. Based on this, the study aimed to enroll 50 patients so that 46 would have 6-month follow-up. Power calculator for continuous outcome non−inferiority trial was based on a program by Sealed Envelope Ltd 2012 (https://www.sealedenvelope.com/power/continuous-noninferior/). All statistical analysis was performed using the open-source statistical package JASP 0.8.6.0. for Microsoft Windows (February 28, 2018).

Results

Forty-nine patients were consented from July 2015 to April 2018 and randomized, 25 to intradiscal oxygen-ozone, and 24 to microdiscectomy. The overall patient flow for the trial arms is detailed in Fig. 4. Forty-three patients (88%) were treated according to their randomization (24 intradiscal oxygen-ozone, 19 microdiscectomy) and constituted the AT group. Prior to treatment, 6 patients randomized dropped out of the study. Five patients randomized to surgery dropped out, 4 reconsidered their participation, and one discontinued due to pregnancy occurring prior to surgery. One subject randomized to oxygen-ozone therapy dropped out because of improvement in the 3-month period between randomization and the scheduled treatment.

Patient characteristics

Patient characteristics are detailed in Table 2. More males than females were included in both study groups and patient average ages were 39.5±10.5 years in the oxygen-ozone group and 41.1±12.9 years in the microdiscectomy group. The majority were active in the work force and a few (4 patients) were unable to work due to their pain. Over half (55%) of patients had been experiencing their current high intensity leg pain (7.0 NRS pain score) for 6 months or longer. Patients in the oxygen-ozone group had undergone a longer period of conservative care - greater than 3 months for 54% of oxygen-ozone and 39% of discectomy patients. Overall, there were no statistically significant differences in any baseline characteristics between the two groups.

Procedural outcomes

Procedural outcomes are detailed in Table 3. Intradiscal oxygen-ozone injections were all technically successful. They were performed under local anesthesia in all but the first 5 cases in Italy, which subsequently transitioned from light sedation, and local anesthesia to local anesthesia only. All microdiscectomies were also technically successful and performed under general anesthesia. In the oxygen-ozone procedures, a mean total of 13.9 mLs was injected — 9.9±2.3 mLs intradiscally, and 4.0±1.9 mLs in the foraminal space. In microdiscectomy, a mean 3.3 cc of disc material was removed through a mean incision of 3.2 cm.

Intradiscal oxygen-ozone procedures were completed in significantly less time than microdiscectomy (35±22 minutes vs. 93±42 minutes; p<.001). Patients were also discharged significantly sooner after oxygen-ozone treatment (p<.01). The mean duration from procedure time to discharge was 4.3±2.9 hours for oxygen-ozone versus 44.2±20.9 hours for microdiscectomy. There were no intra- or post-operative complications associated with either procedure.

Clinical outcomes

In the 6-month follow-up, 2 patients in the microdiscectomy group had unrelieved leg pain, and underwent subsequent procedures. One patient received a second microdiscectomy at 3 months, did not improve, and withdrew from the study. The other patient, improving after a percutaneous disc coblation procedure at 6 months, remained in the study.

In the intradiscal oxygen-ozone group, 8 patients (33%) had unrelieved leg pain and seven of the eight went on to have microdiscectomy (29%) within the 6-month follow-up. Six having microdiscectomy improved, five remained in the study, and one withdrew from the study after their first post-operative visit. Of the 2 patients not improving with microdiscectomy, one improved in back pain but not leg pain scores, and withdrew from the study. The other patient, after doing well through the first month, had a poor 3-month outcome was given a foraminotomy (4%) to remove bony compression, and did not return after the surgery.

The results of the primary treatment endpoint of improved leg pain over 6 months are provided in Table 4. This analysis was performed using both the AT population (43 patients) and repeated using the ITT population (49 patients). The between group treatment difference in 6-month mean leg pain improvement, in the AT analysis was in favor of microdiscectomy by 0.31 points, and in the ITT, analysis was in favor of oxygen-ozone by 0.32 points. Intradiscal oxygen-ozone did not exceed the non−inferiority margin or difference of -1.94 in the primary outcome in either the AT or the ITT analyses. The lower limit of a one-tailed 95% confidence interval for the 6-month treatment

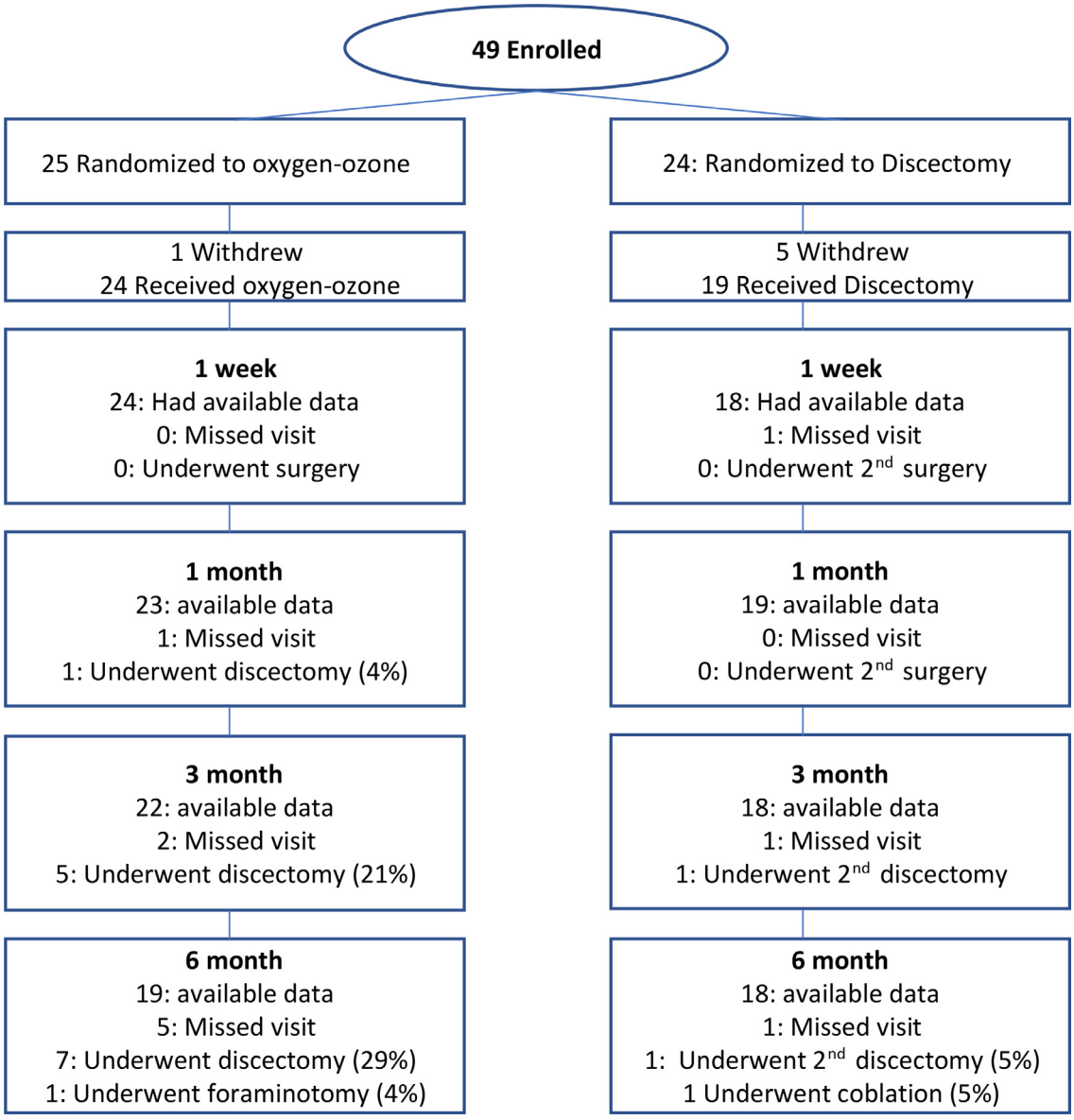

Fig. 4. Flow diagram for patients randomized to intradiscal oxygen-ozone or microdiscectomy for primary single level lumbar disc herniation radiculopathy.

difference was -1.72 for the AT and -1.13 for the ITT population. Sensitivity analyses performed by adding covariates into the ANCOVA model did not alter the non−inferiority of the primary analysis. Post-hoc analyses evaluating improvements in leg pain over baseline at each follow-up point using baseline leg pain as covariate were also detailed in Table 4.

Overall, both treatment groups demonstrated marked improvement in all clinical outcomes, and there were no statistically significant differences between treatment groups based on repeated measures ANOVA for the AT population. Leg pain mean scores rapidly and significantly ($p<.001$) improved over baseline in both treatment groups and persisted throughout 6-month follow-up (Fig. 5). Back pain mean scores, also significantly ($p<.001$) improved although baseline values were less compared to leg pain scores (Fig. 6). The RMDI disability scores also rapidly and significantly ($p<.001$) improved over baseline and continued to improve in follow-up (Fig. 7). Overall health on the EQ-5D significantly improved in both groups and improvements were noted in all five subdomains (pain, self-care, activity, mobility, and anxiety) although anxiety was the least affected health outcome (Fig. 8). There were no significant differences between groups for any of the subdomains.

Tolerance and safety

All procedures were successfully performed and there were no procedural-, device-, or surgery-related adverse events. All patients in the oxygen-ozone group were

Table 2
Characteristics of subjects enrolled and completing baseline assessments

	Intradiscal oxygen-ozone	Microdiscectomy	p value
Gender	7 Female; 17 Male	9 Female; 14 Male	.52
Age	39.5 (SD, 10.5)	41.1 (SD, 12.9)	.70
BMI	27.8 (SD, 5.68)	25.8 (SD, 3.31)	.74
Current smoker	14 No; 10: Yes	18 No; 5 Yes	.14
History of smoking, in non−smokers	11 No; 3 Yes.	14 No; 4 Yes	.96
Type of work	Manual Labor: 11	Manual Labor: 9	.91
	Standing and/or walking: 3	Standing and/or walking: 4	
	Sedentary: 5	Sedentary: 4	
	Not working: 5	Not working: 6	
Work status	Full-time: 11	Full-time: 10	.54
	20−40 h/wk: 5	20−40 h/wk: 3	
	<20 h/wk: 2	<20 h/wk: 2	
	Retired and/or Chose not to: 3	Retired and/or Chose not to: 7	
	Cannot due to pain: 3	Cannot due to pain: 1	
Disc hernia lumbar level	L1-L2: 0	L1-L2: 0	.53
	L2-L3: 0	L2-L3: 1	
	L3-L4: 0	L3-L4: 1	
	L4-L5: 11	L4-L5: 9	
	L5-S1: 13	L5-S1: 12	
Side of herniation	Left: 16; Right: 8	Left: 9; Right: 13	.13
Duration of conservative care	none: 0	none: 1	.54
	4−12 wk: 11	4−12 wk: 13	
	12 wk−6mo: 7	12 wk−6mo: 4	
	6−12 mo: 3+12 mo: 3	6−12 mo: 4+12 mo: 1	
Back pain intensity, NRS	4.3 (SD, 3.29)	5.0 (SD, 3.05)	.63
Leg pain intensity, NRS	7.6 (SD, 1.08)	7.8 (SD, 1.8)	.37
Duration of this episode of leg pain	6−8 wk: 0 8 wk-6 mo: 13 6-12 mo: 8+12 mo: 3	6−8 wk: 18 wk-6 mo: 13 6-12 mo: 3+12 mo: 6	.24
Total history of leg pain	6−8 wk: 0 8 wk-6 mo: 11 6-12 mo: 5+12 mo: 8	6−8 wk: 1 8 wk-6 mo: 9 6-12 mo: 4+12 mo: 9	.72

Note. p-values from Chi-squared test comparing baseline differences in categorical outcomes and Mann-Whitney *U* test comparing baseline difference in numerical outcomes

discharged on the same day and there were no extended stays for patients in the surgery group. There were no post-operative re-admissions for patients in either treatment group. The most frequent adverse events in both groups were leg and/or back pain, which were managed at the discretion of the treating physician. Overall, 25% of patients (six oxygen-ozone, four microdiscectomy) received subsequent spinal nerve blocks or infusions in follow-up for post-operative pain, persistent, or aggravated leg or back pain. There were no significant differences between treatment groups in spinal blocks performed.

Discussion

Main findings

This is the first RCT to compare intradiscal oxygen-ozone therapy to microdiscectomy for primary single- level

Table 3
Treatment procedural-related outcomes

	Intradiscal oxygen-ozone	Microdiscectomy	p value
Time (min) in operating room (mean, SD)	35 (SD, 22)	93 (SD, 42)	<.001
Type of anesthesia	19: Local	0: Local	<.001
	5: Light sedation*	0: Light sedation	
	0: General	19: General	
Amount (mL) of gas injected to disc space (mean, SD)	9.9 (SD, 2.3)	NA	
Amount of gas (mL) injected to foraminal space (mean, SD)	4.0 (SD, 1.9)		
Time (s) to complete oxygen-ozone injection procedure (mean, SD)	349 (SD, 276)	NA	
Amount of disc material (cc) removed (mean, SD)	NA	3.3 (SD, 1.2)	
Estimated mL blood loss (mean, SD)	NA	53 (SD, 55)	
Length (cm) of incision (mean, SD)	NA	3.3 (SD, 1.1)	
H from end of procedure to discharge (mean, SD).	4.3 (SD, 2.9)	44.2 (SD, 29.9)	<.001

Abbreviations: NA, not applicable; SD, standard deviation

* First 5 cases performed in Italy, which then transitioned to local anesthesia. p-values from Mann-Whitney *U*-test

Table 4
Evaluation of the non−inferiority of the primary endpoint, improvement in leg pain over six months

	Primary analysis	
	Weighted average leg pain score, 1 wk through 6 mo. (ANCOVA)	
	As-Treated	Intent to Treat
Microdiscectomy (mean, SE)	2.78 (SE, 0.62)	3.62 (SE, 0.64)
Intradiscal oxygen-ozone (mean, SE)	3.09 (SE, 0.55)	3.31 (SE, 0.61)
Difference in weighted average leg pain score, 1 wk through six mo, adjusted for leg pain at baseline (ANCOVA) (mean, SE, LL)	-0.31 (SE, 0.84) 95% LL=-1.72 points	0.32 (SE, 0.88) 95% LL=-1.13 points
	Post Hoc analyses	
Change from baseline to 1 wk Mean (SE), LL	-1.53 (SE, 0.90). LL=-3.05	-0.94 (SE, 0.90). LL=-2.42
Change from baseline to 1 mo Mean (SE), LL	0.03 (SE 0.92). LL=-1.52	0.58 (SE, 0.93). LL=-0.96
Change from baseline to 3 mo Mean (SE), LL	-0.02 (SE, 0.98). LL=-1.67	0.50 (SE, 1.00). LL=-1.15
Change from baseline to 6 mo Mean (SE), LL	-0.47 (SE, 0.93). LL=-2.04	0.23 (SE, 0.95). LL=-1.35

Note: Primary analysis, involved a non−inferiority margin of -1.94 points. 'LL' is the Lower Limit of the one-tailed 95% confidence limit on the difference between groups and it is compared to the non−inferiority margin. LL less than -1.94 supports the conclusion of non−inferiority.

Post Hoc analyses: Mean and standard error on the difference in improvement at each follow-up visit, using baseline leg pain as a covariate. The lower limits (LL) of the one-tailed 95% confidence limits are also provided.

lumbar disc herniation refractory radicular leg pain. Both treatments produced statistically significant improvements in validated clinical outcomes that persisted and there were no between group differences. Additionally, a formal non−inferiority test with both ITT and AT populations, supported intradiscal oxygen-ozone therapy as a non−inferior treatment to microdiscectomy for a primary outcome of overall 6-month leg pain improvement. During the 6-month follow-up, 71% of patients undergoing intradiscal oxygen-ozone were able to avoid a discectomy.

Treatment effectiveness

The rapid and significant reductions of leg pain and functional disability for both treatment groups in this RCT are consistent with results reported by numerous clinical studies. Treatment effectiveness of intradiscal oxygen-ozone for lumbar disc herniation leg pain is consistent with results in numerous large prospective cohort studies ranging from over 200 to almost 3,000 patients − Lehnert et al. (n=283) [45], Leonardi et al. (n=600) [61], Oder et al. (n=612) [62], D'Erme et al. (n=1,000) [63], and Muto et al. (n=2,900) [42]. Although the 6-month follow-up in this trial was short, long-term effectiveness (follow-up beyond one year) of oxygen-ozone for lumbar herniated disc radiculopathy has also been reported in several clinical cohorts [32,64,65].

The effectiveness of traditional open microdiscectomies performed in this RCT is also consistent with improvements in short-term clinical outcomes reported in numerous systematic reviews of lumbar microdiscectomy studies [66−71]. In this RCT, re-operations after microdiscectomy were performed for 2 patients (8.7%), and repeat discectomies for 1 patient (4.3%) in 6-month follow-up. Rates reported in the reviews for lumbar disc reherniations (range, 4.6%−5.2%) and reoperations (range, 5.9%−11.8%) were generally consistent with those for open microdiscectomy in this RCT. In the reviews, these rates for open microdiscectomy were also compared with various more minimally invasive surgical approaches, and were generally lower, although not significantly, than the comparator minimally invasive surgical approaches.

Study design

A non−inferiority design was chosen for the trial because although treatment with intradiscal oxygen-ozone therapy was thought to be less effective than microdiscectomy, it potentially afforded several advantages for patients. Intradiscal oxygen-ozone therapy is a less expensive and less invasive therapy than microdiscectomy. The injection also has procedural advantages, does not involve changes to the bony anatomy, and preserves all future surgical options. Avoiding microdiscectomy was a secondary outcome of the RCT.

Some of the advantages for intradiscal oxygen- ozone were shown in the trial. The procedures were performed in an outpatient setting without general anesthesia and patients recovered more quickly and were discharged earlier than those undergoing microdiscectomy. Patients in the oxygen-ozone group were discharged the same day and those undergoing microdiscectomy had a 1- to 2-day hospital stay. Hospital stays after lumbar discectomy have also been extensively reviewed and variable mean stays have been reported − 3.3 to 12.0 days [66], 3.3−4.4 days [68], 6.8 days [69] and 3.8−15.6 days [70]. Many factors may influence duration of hospital stay and the short hospital stays for patients undergoing microdiscectomy in this RCT, may be related to the study population who were younger, still working, and without major comorbidities.

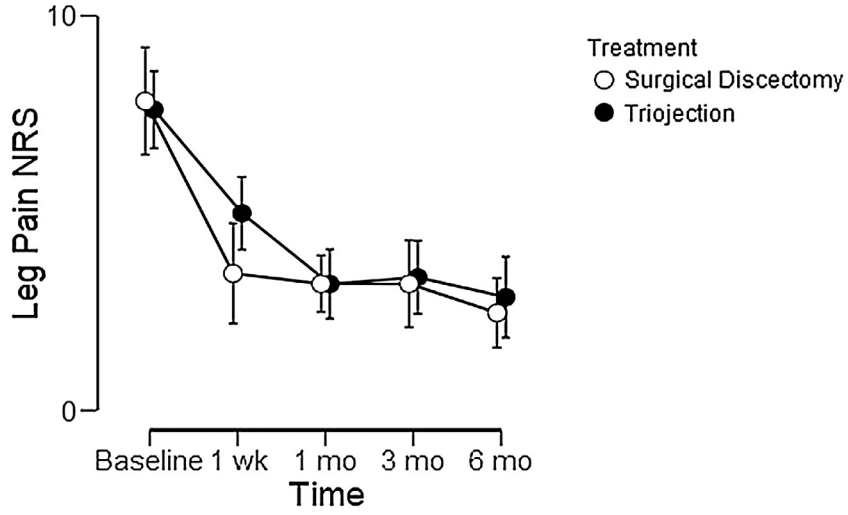

Fig. 5. Leg pain scores through six months. NRS, 0 is no pain, and 10 is maximum pain. Means and 95% confidence limits are shown. Time effect was significant (p<.001). Treatment difference between groups was not significant (p=.529). No significant changes after 1 month.

Although complications or adverse events were not found in the trial for either treatment group, the trial was not powered to detect these events after these procedures. Although not shown in this small RCT, the lower 0.6% overall complication rate [72] reported in the literature for intradiscal oxygen-ozone therapy compared to the 7.6% [73], and 12.5% [74] overall complication rate for microdiscectomy surgeries, is advantageous for patients. Patients are also easily able to have an additional oxygen-ozone injection, or have a later microdiscectomy, if they did not sufficiently respond to their initial oxygen-ozone treatment.

Non–Inferiority margin

Intradiscal oxygen-ozone did meet the pre-specified non–inferiority margin to microdiscectomy for the primary outcome of 6-month leg pain improvements in patients with single-level contained lumbar disc radiculopathy. A primary endpoint at 6-month follow-up was chosen as the optimal time to detect differences between interventions, if they existed. It was also chosen to avoid an equivalence situation that could artificially arise over longer periods of follow-up when outcomes of the interventions stabilize or the natural history of the condition tends to equivalence. Defining a non–inferiority margin for treatment success is a key element of a non–inferiority trial and is based on both clinical and statistical considerations [75]. Clinical considerations are that a maximum treatment differences between groups, or the loss of treatment efficacy, would be clinically acceptable. Statistical considerations are that the margin would be small enough to protect against a positive finding for a treatment that is no better than placebo.

There is flexibility and no consensus on how to set non–inferiority margins for non–inferiority trials [75,76]. The non–inferiority margin for this trial was based on the fixed-

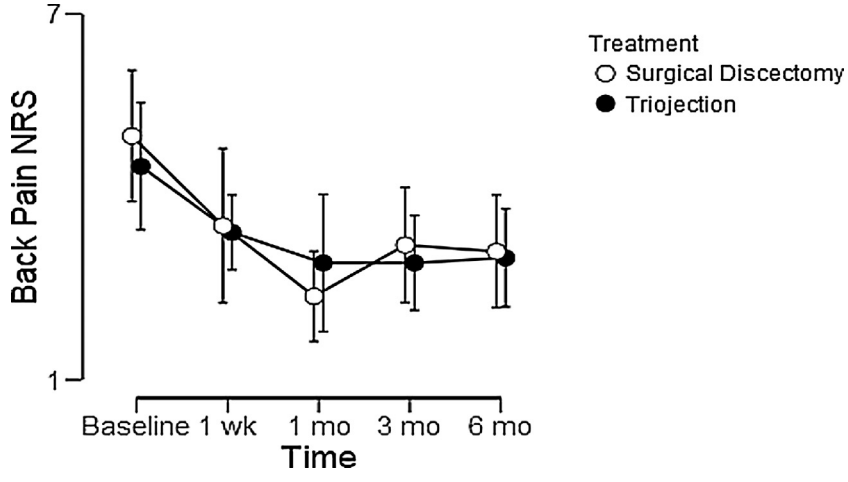

Fig. 6. Back pain scores through 6 months. NRS, 0 is no pain, and 10 is maximum pain. Means and 95% confidence limits are shown. Time effect is significant (p<.001) while treatment difference between groups is not (p=.899).

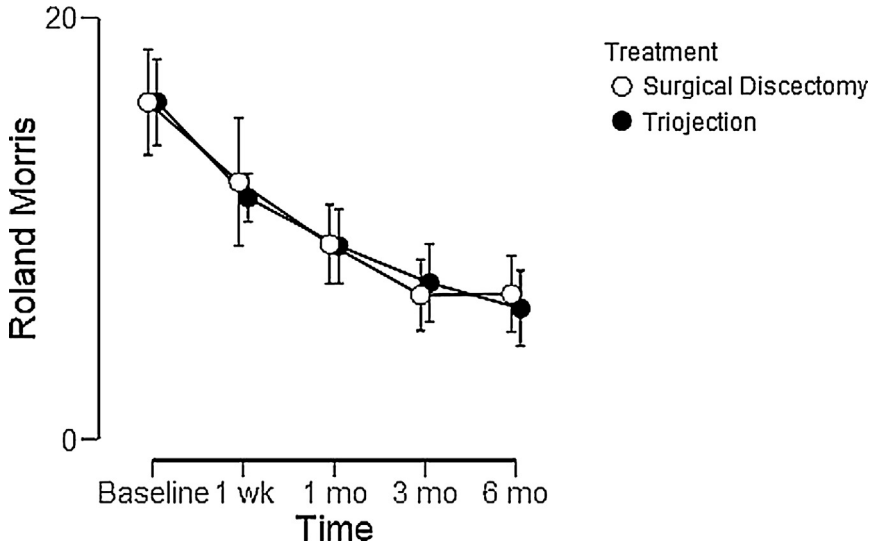

Fig. 7. Roland Morris Disability Index scores through 6 months. 0 is no disability and 24 is complete disability. Means and 95% confidence limits are shown. Time effect was significant (p<.001) while treatment difference between groups was not (p=.566).

margin method recommended by the FDA that defines the margin based on the smallest effect size expressed as the lower limit of the confidence interval of the comparators with microdiscectomy [77]. In addition, the margin was based on a preservation of 50% of expected benefit of microdiscectomy. There is precedent for such a level as both the FDA and European Medicines Agency regulatory bodies have stated a 50% preserved fraction of benefit can be an acceptable tolerance for loss of treatment benefit under several conditions [77,78]. Some of the conditions for this acceptance include: a non−lethal disease, high degree of effectiveness for the standard treatment (microdiscectomy), other advantages or a better safety profile for the alternate treatment (intradiscal oxygen-ozone). All of these conditions are satisfied for lumbar disc herniation radiculopathy and the treatments in the trial.

The sample size calculation for the trial involved the non−inferiority margin and choice of 5% alpha error, a type I decision probability error that a treatment would be found non−inferior when it actually was. Although a more stringent 2.5% alpha level could have been employed, it only marginally increased the sample size. However, a small sample size for a non−inferiority trial potentially increases the risk of a decision error of accepting a non−inferiority status for a treatment. The fidelity of the results of the non−inferiority status of intradiscal oxygen-ozone was supported by further investigations. Non−inferiority status was unaffected by sensitivity analyses involving multiple covariates and was confirmed in both ITT and AT populations. In addition, the full distribution of mean scores and 95% confidence intervals of each treatment group were graphically displayed for multiple validated pain, disability, and quality-of-life outcome scores. Differences between the treatment groups were not statistically significant at any follow-up point and the curves were virtually overlapping for the two treatment groups.

Study randomization

The RCT was a multicenter study conducted in several European sites increasing the generalizability of the findings. Randomization was a stratified block design ensuring equal participation across sites. However, blinding of the interventionalists or patients to their study treatments was not possible as the interventions were performed by different specialists in different procedural settings. Nevertheless, several methodological safeguards were made to minimize the effects of potential bias. The implementation of the randomization procedure was performed off site independently by the study statistician. Concealment of allocation was achieved during the process of creating trial groups in that the randomization procedure involved the creation of a randomization schedule using a computerized random number generator for each site. Treating physicians were unaware of treatment allocations of patients as assignments were only provided after their randomization requests. In addition, follow-up, and data collection were conducted with use of clinical research outcome assessors who were blind to the treatment assignment of patients. Outcome assessments also involved multiple validated measurement instruments of pain, disability, and quality-of-life.

Patient selection

The selection of patients with the best chance for a successful procedure is essential not only for the valid assessment of effectiveness of interventions but also for decisions to be made in everyday clinical practice. A strength of the

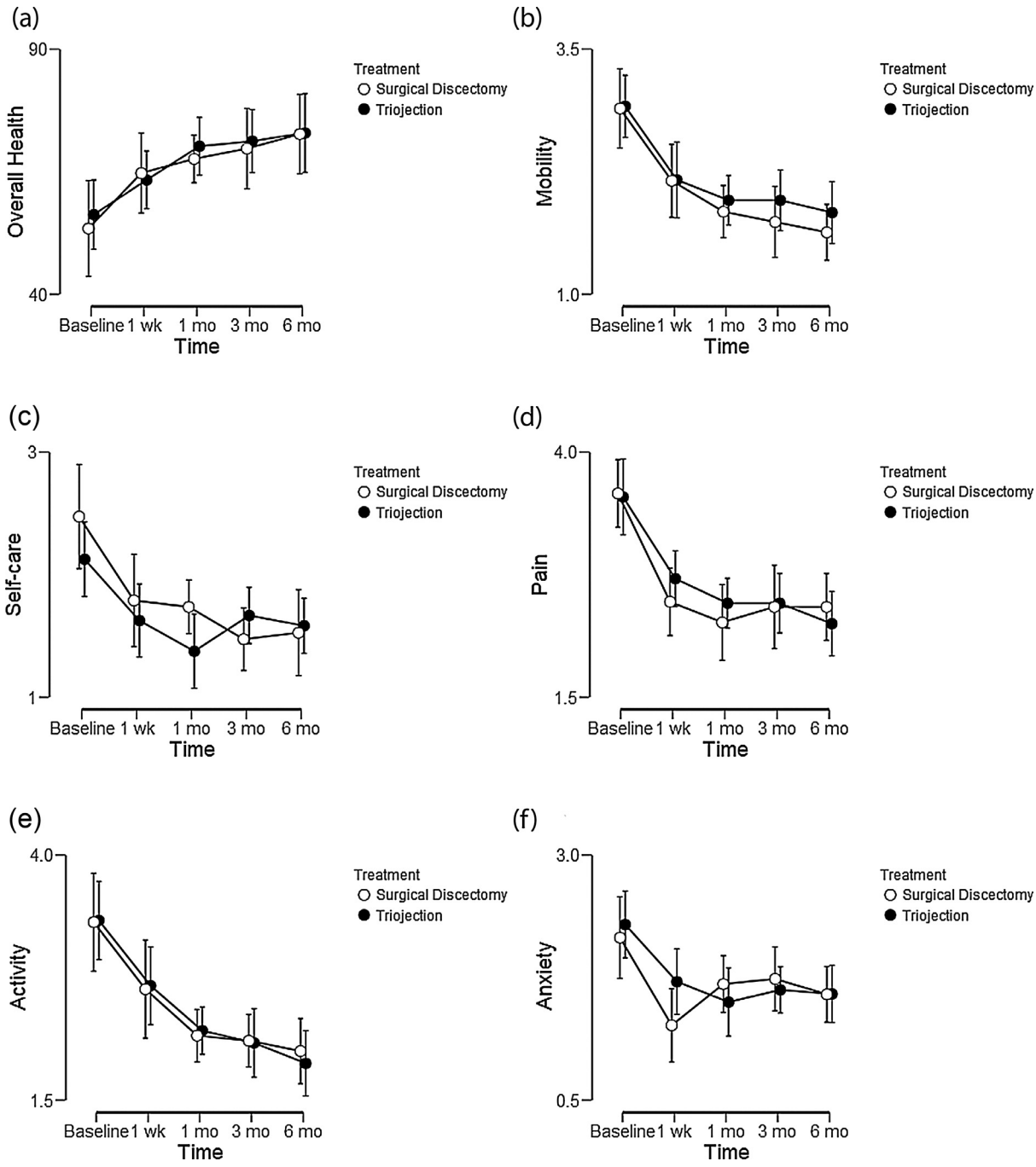

Fig. 8. Dimensions of the EQ-5D. Overall Health is scored 0–100. All other dimensions are scored 1–5. Means and 95% confidence intervals. Repeated measures of analysis of variance identified a time effect but no significant effects or interactions involving treatment group.

trial was the rigorous quantitative MRI criteria assessed by experienced neuroradiologists to select patient eligibility for the trial. MRI is recognized as the gold standard for evaluating relationships between disc material to soft tissue and neural structures [79,80]. The MRI criteria for the trials' inclusion, including nerve compression due to disc herniation [81–84], loss of disc height, and signal intensity [85,86] have all been shown to be reliable quantitative measures. These criteria have also been shown to have a corresponding relationship with lumbar degenerative discs [79,87]. In addition to the radiologic criteria, a clinical assessment, and dermatologic distribution of pain consistent with the radiologic findings was required.

The multicenter trial involved a lengthy patient accrual period and we did not track the number of patients eligible for the study. Enrollment took longer than anticipated with

the strict enrollment criteria and patient preference being factors. Many patients were unwilling to be randomized given an equal chance of surgery rather than oxygen-ozone treatment. On the other hand, there were subjects who felt they had exhausted all conservative measures, and wanted to proceed directly to surgery. Although the randomization process resulted in the majority of patients (89%) receiving their allocated treatment assignment, there were more patient withdrawals (five vs. one) for those randomized to microdiscectomy suggesting a patient preference for a more minimally invasive treatment. There were also few patients lost to follow-up, but 7 patients (29%) in the oxygen-ozone group crossed over to microdiscectomy for inadequate symptom relief, almost all (6 patients) within the 3- month follow-up.

A potential limitation of the study is that the surgical procedure was left to the discretion of participating surgeons and traditional open microdiscectomy procedures were employed at the sites. However, a review of the literature shows that treatment effectiveness of open microdiscectomy for lumbar disc herniation was similar to more minimally invasive surgical approaches, and that rates of reoperations were often lower. This RCT was not powered to detect adverse events and the small study size limits estimates of safety for both treatments. Although a clinically significant surgical avoidance rate for patients with herniated lumbar disc radiculopathy has not been established, confirming the high avoidance rate with intradiscal oxygen-ozone in this trial with larger, and longer follow-up clinical trials would provide additional valuable information.

Conclusions

This was the first RCT comparing intradiscal oxygen-ozone injection to microdiscectomy for primary single-level lumbar disc herniation refractory radicular leg pain. Both intradiscal oxygen-ozone and microdiscectomy resulted in rapid and statistically significant improvements in leg pain, disability, and quality of life that persisted in follow-up. Intradiscal oxygen-ozone therapy did not exceed the non −inferiority margin and improvements in 6-month leg pain were not less than those with microdiscectomy. Overall, 71% of patients undergoing oxygen-ozone intradiscal were able to avoid microdiscectomy. Patients with selected lumbar herniated disc radicular leg pain, unresponsive to conservative management, may be offered oxygen-ozone treatment as an effective treatment prior to microdiscectomy.

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Declarations of Competing Interests

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found in the online version at https://doi.org/10.1016/j.spinee.2021.11.017.

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