Observational Study

α-Lipoic Acid, Palmitoylethanolamide, Myrrh, and Oxygen-Ozone Therapy Improve Pharmacological Therapy in Acute Painful Lumbosacral Radiculopathy due to Herniated Disc

Eleonora Latini, MD, Giulia Bonasia, MD, Ludovica Petroselli, MD, Melissa Mazzola, MD, Francesca Musa, MD, Flavia Santoboni, MD, Donatella Trischitta, MD, Maria Nusca Sveva, MD, PhD, Mario Vetrano, MD, PhD, and Maria Chiara Vulpiani, MD

From: Physical Medicine & Rehabilitation Unit, Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea University Hospital, Sapienza University of Rome, Rome, Italy

Address Correspondence:
Eleonora Latini, MD
Physical Medicine & Rehabilitation Unit, Department of Medical and Surgical Sciences and Translational Medicine, Sant'Andrea University Hospital
Sapienza University of Rome
00189 Rome, Italy
E-mail:
dott.eleonoralatini@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 09-16-2022
Revised manuscript received: 01-19-2023
Accepted for publication: 03-06-2023

Free full manuscript:
www.painphysicianjournal.com

Background: Neuropathic mechanisms largely contribute to radicular Low Back Pain (LBP) and an increase in oxidative stress is recognized as one of the possible causes of nerve damage, inducing axonal degeneration and myelin degradation of nerve fibers.

Objectives: We investigated whether a combination of nutraceutical supplements and oxygen-ozone (O_2-O_3) therapy might reduce disability and improve clinical effects of pharmacological therapy in patients with acute radicular LBP.

Study Design: This is a prospective, open-label, comparative observational study approved by the Institutional Review Board of the Sapienza University of Rome (RS 6285/2021).

Setting: Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital.

Methods: Within the scope of this study, 62 patients with acute radicular LBP diagnosed with disc herniation were assigned into 4 groups. The first group was assigned pharmacological therapy (n = 16), the second group was assigned pharmacological therapy and nutraceutical supplements (n = 15), the third group was assigned pharmacological therapy and O_2-O_3 therapy (n = 15), and the fourth group was assigned pharmacological therapy, nutraceutical supplements, and O_2-O_3therapy (n = 16). All patients who participated in the study were evaluated at the beginning of the study, 2 weeks, and 4 weeks (T2) after the beginning of treatment using the Numeric Rating Scale (NRS-11), Oswestry Disability Index (ODI), and 12-item Short-Form Health Survey. Opioid analgesic intake was noted from baseline to end of treatment (T2).

Results: In each group was observed a statistically significant difference for all measures compared to the baseline. At the T2 evaluation time between groups for the Mann-Whitney U test, a statistically significant difference was found: in the ODI scale between groups B and A ($P = 0.004$), groups C and A ($P < 0.001$), and groups D and A ($P < 0.001$); in the NRS-11 between groups B and A ($P = 0.017$), groups C and A ($P = 0.002$), and groups D and A ($P < 0.001$); in the 12-item Physical Component Summary score between groups B and A ($P = 0.003$), groups C and A ($P = 0.002$), and groups D and A ($P < 0.001$), while no significant differences between groups were observed in the 12-item Mental Component Summary score. The average days of opioid usage were similar in the 4 groups (8.33 in group A, 8.33 in group B, 8.33 in group C, and 8.75 in group D). However, the percentage of patients requiring adjuvant opioid therapy differed remarkably: 60% in group A, 40% in group B, 20% in group C, and 25% in group D.

Limitations: A small number of patients were recruited, and we did not perform long-term follow-up.

Conclusions: This study supports a multimodal approach combining nutraceutical supplements and O_2-O_3 therapy with pharmacological therapy in the treatment of acute radicular LBP secondary to disc herniation. The combination of neurotrophic and antioxidant therapies represents an etiopathogenetic approach, not purely symptomatic, that reduces symptomatology and avoids progression of the nerve damage.

Key words: Low back pain, lumbar radicular pain, neuropathic pain, herniated disc, alpha lipoic acid, palmitoylethanolamide, myrrh, oxygen-ozone therapy, ozone, nutraceuticals

Pain Physician 2023: 26:E363-E373

Acute painful lumbosacral radiculopathy is a relatively common musculoskeletal complaint caused by the compression or irritation of a spinal nerve due to lumbar disc herniation or spinal stenosis (1). Symptoms include axial low back pain (LBP) radiating into the lower limbs, sensory loss or paraesthesia, numbness, and motor weakness (2). Its prevalence rate in patient populations is approximately 3% to 5%, without gender predominance (3). Although many conservative approaches have been developed, the pharmacological analgesic therapy (e.g., analgesics, nonsteroidal anti-inflammatory drugs [NSAIDs], opioid analgesics, corticosteroids, muscle relaxants, antidepressants, and anticonvulsants) forms the mainstay of treatment (4,5). However, the efficacy and tolerability of commonly prescribed analgesic and adjuvant drugs have not been well established and there are no general recommendations and clear guidelines (6). So that the management of acute lumbosacral radiculopathy remains a major concern.

Neuropathic mechanisms largely contribute to lumbosacral radiculopathy and an increase in oxidative stress is recognized as one of the possible causes of nerve damage, inducing axonal degeneration and myelin degradation of nerve fibers. Oxidative stress that develops after a peripheral neuropathic lesion leads to the activation of an inflammatory pathway involving the whole peripheral nerve and is responsible for pain and loss of nerve conduction functionality (7,8). Alpha-lipoic acid (ALA, thioctic acid) has been recently proposed for the treatment of patients with peripheral nerve injuries (9). Its potent oxidant scavenging (10), and anti-inflammatory properties has been recognized as part of the mechanism underlying the clinical benefits observed in treatment of diabetic neuropathy (11-14), radiculopathy syndrome caused by herniated disc (15), and other types of neuropathies, such as carpal tunnel syndrome (16). Other potential analgesic therapies are emerging, including myrrh and palmitoylethanolamide (PEA), an endogenous compound, involved in the resolution of inflammatory processes and neuroprotection (17-20). Lastly, oxygen-ozone (O_2-O_3) therapy has been suggested as a therapeutic strategy for LBP thanks to its potential analgesic, anti-inflammatory, antioxidant, and immunomodulating action (21), showing a level of evidence of II-1 in the treatment of back pain secondary to herniated disc with a grade of recommendation 1B (22). It has also been defined as "acupuncture chemistry" because the injection of the gaseous mixture and the needle puncture play a role in inducing a series of complex chemical and neurological reactions that lead to the disappearance of pain in the majority (i.e., positive responses in 70% to 80% of cases) of patients with LBP (23).

Since neuroinflammation, oxidative stress, and nociceptive factors play a pathogenetic role in acute lumbosacral radiculopathy, we investigated whether a combination of neurotrophic/antinociceptive nutraceutical supplements and O_2-O_3 therapy might reduce disability and improve clinical effect of pharmacological therapy in these patients.

Methods

This is a prospective, open-label, comparative observational study approved by the Institutional Review Board of the Sapienza University of Rome (RS 6285/2021) and conducted according to good clinical practice and the ethics of the Helsinki declaration (24).

Sample Size Calculation

We assumed a standard deviation change in the Oswestry Disability Index (ODI) of 15 and a minimum clinically important difference on the ODI of 8.0 (25). At 5% level of significance and 80% power of test, ß of 0.2, the sample size was calculated as 14 patients per group. An additional 5% was added to compensate for the patients lost to follow-up. Hence, the sample size was calculated to be 15 patients in each group.

Eligibility Criteria and Enrollment

The recruitment took place, from April 2021 to March 2022, at the Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital, Rome, Italy. Patients of both genders with acute lumbosacral radiculopathy were eligible.

Inclusion criteria were as follows: age 18-75 with an acute painful lumbosacral radiculopathy for < 3 months; moderate or severe intensity of pain (Numeric Rating Scale: NRS-11 ≥ 6); and diagnosis of lumbar disc herniation confirmed with magnetic resonance imaging or computed tomography studies of the lumbosacral spine, related to clinical presentation.

Exclusion criteria were as follows: pain lasting > 3 months; severe motor neurological deficit; cauda equina syndrome; other spinal disorder as lumbar spinal stenosis, lumbar spondylolisthesis, ankylosing spondylitis, or spinal tuberculosis; previous lumbar surgery; contraindications for corticosteroids; any contraindication to paravertebral infiltrative therapy with O_2-O_3, such as pregnancy, glucose-6-phosphate dehydrogenase deficiency (favism), uncontrolled hyperthyroidism, severe cardiovascular diseases, and heart failure; any condition where spine surgical treatment is recommended; and diabetes mellitus.

During the assessment, the study was explained in detail, and the inclusion and exclusion criteria were evaluated. Eligible patients who agreed to participate signed a written informed consent. The proposed patient flow through the study is shown in Fig. 1.

After completing the baseline data, eligible patients were assigned to the study groups according to their medical history, and clinical and instrumental evaluations. The outcome measures were administered at baseline (T0), 2 weeks (T1), and 4 weeks (T2) after the beginning of treatment, coinciding with the end of treatment. The assessments at T0, T1, and T2 were carried out by the same physiatrist.

Study Procedure

A total of 62 patients with acute lumbosacral radiculopathy were assigned to 4 treatment groups: group A received a pharmacological therapy; group B received a combination of pharmacological therapy and nutraceutical compounds; group C received a combination of pharmacological therapy and paravertebral intramuscular O_2-O_3 therapy; and group D received a combination of pharmacological therapy, nutraceutical supplements, and paravertebral intramuscular O_2-O_3 therapy (Table 1).

Pharmacological Therapy

All patients received a pharmacological therapy with corticosteroid drugs. Two milliliters of betamethasone disodium phosphate 4 mg/2 mL was administered intramuscularly twice daily during the first week and once daily during the second week; then 2 tablets of betamethasone disodium phosphate 1 mg were ad-

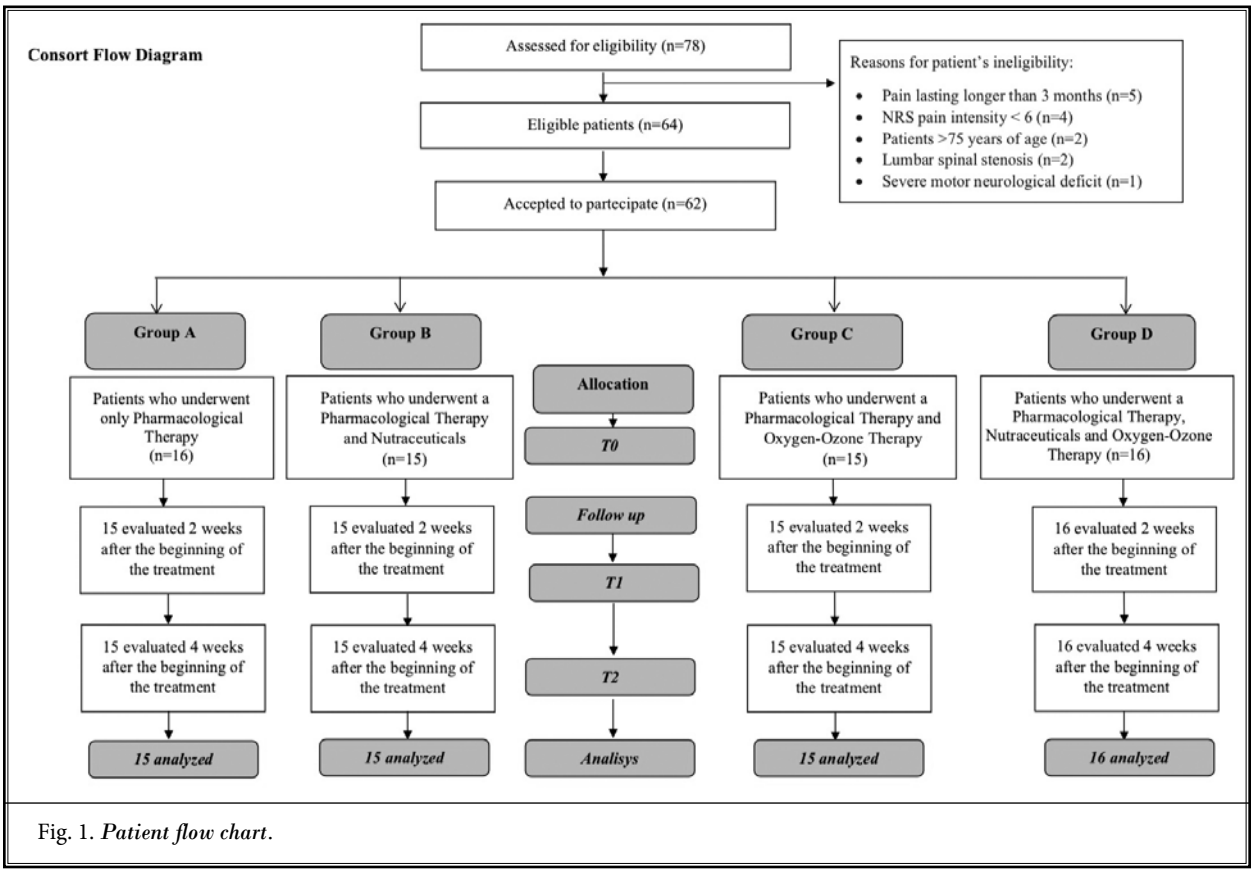

Fig. 1. *Patient flow chart*.

Table 1. *Demographic and clinical characteristics in study patients at baseline.*

Baseline Characteristics	Total (n = 62)	Group A (n = 16)	Group B (n = 15)	Group C (n = 15)	Group D (n = 16)	*P* value
Age, mean (SD) years	51.40 (12.71)	53.69 (10.09)	52.8 (11.56)	50.6 (13.65)	48.56 (15.49)	0.704
Gender:						
Women, n (%)	24 (38.7)	9 (56.3)	5 (33.3)	7 (46.7)	3 (18.7)	0.148
Men, n (%)	38 (61.3)	7 (43.7)	10 (66.7)	8 (53.3)	13 (81.3)	
Weight, mean (SD) kg	73.60 (13.37)	73.44 (17.32)	74.13 (11.87)	72.4 (12.66)	74.38 (11.97)	0.898
Height, mean (SD) cm	173.21 (9.74)	171.2 (8.69)	173.0 (10.8)	172.07 (7.9)	176.5 (11.18)	0.383
BMI (kg/cm^2), mean (SD)	24.44 (3.49)	24.96 (5.32)	24.65 (1.99)	24.42 (3.66)	23.74 (2.06)	0.664
Disc Herniation:						0.397
L1-L2, n (%)	2 (3.2)	0 (0.0)	2 (13.3)	0 (0.0)	0 (0.0)	
L2-L3, n (%)	1 (1.6)	1 (6.3)	0 (0.0)	0 (0.0)	0 (0.0)	
L3-L4, n (%)	4 (6.5)	0 (0.0)	1 (6.7)	2 (13.3)	1 (6.3)	
L4-L5, n (%)	21 (33.9)	5 (31.3)	6 (40.0)	4 (26.7)	6 (37.5)	
L5-S1, n (%)	34 (54.8)	10 (62.5)	6 (40.0)	9 (60%)	9 (56.3)	
Outcome Measures						
NRS-11, mean (SD)	8.40 (1.25)	8.44 (0.96)	8.53 (1.46)	8.33 (1.29)	8.31 (1.35)	0.954
ODI, mean (SD)	55.78 (14.40)	53.54 (13.06)	55.62 (16.73)	56.35 (11.97)	57.62 (16.38)	0.910
PCS-12, mean (SD)	27.96 (4.99)	28.15 (5.27)	27.25 (6.02)	27.63 (4.85)	28.75 (4.02)	0.838
MCS-12, mean (SD)	41.58 (9.96)	45.29 (11.47)	42.5 (9.05)	43.5 (10.21)	35.22 (5.99)	0.013*

Abbreviations: BMI, body mass index; NRS-11, Numeric Rating Scale; ODI, Oswestry Disability Index; PCS-12, 12-item Physical Component Summary Score; MCS-12, 12-item Mental Component Summary Score; n, number; SD, standard deviation.
*Statistical significance, $P < 0.05$.

ministered orally once daily during the third week. If deemed necessary based on the patient's clinical symptoms, an adjuvant opioid analgesic with oxycodone/naloxone 10 mg/5 mg, respectively, was administered once daily. Adjuvant opioid analgesic therapy could be discontinued by the patient upon subjective improvement of the painful symptoms.

Nutraceutical Supplements

Nutraceutical supplements can be used as adjunct therapies in patients with acute lumbosacral radiculopathy. In this study, a nutraceutical composed (Tiobec® Dol, Uriach Italy Srl) of ALA (404 mg), nonmicronized PEA (non-m-PEA) (306 mg), and myrrh (Commiphora myrrha [Nees] Engl, oleum-gummi-resina) (100 mg), was administered in conjunction with pharmacological therapy (group B) or with pharmacological therapy and O_2-O_3 therapy (group D). Tiobec® Dol was prescribed twice a day for 4 weeks, at least 30 minutes before a meal or 3 hours after (on an empty stomach). The 2 daily intakes were separated by about 10 hours. The registration number for Tiobec® Dol at the Italian Ministry of Health is 80309.

O_2-O_3 Therapy

The O_2-O_3 therapy was used for its analgesic, antioxidant, anti-inflammatory, and immunomodulating properties in conjunction with pharmacological therapy (group C) or with pharmacological therapy and nutraceutical supplements (group D). Patients received a total of 8 O_2-O_3 intramuscular injections, twice a week for 4 weeks. The O_2-O_3 intramuscular injection was administered in the paravertebral muscles corresponding to the metamer of vertebral segment affected. For each treatment session, were performed 2 symmetrical injections of 10 mL of the O_2-O_3 gaseous mixture (15 µg/mL concentration), obtained by means of a Multiossigen Medical 99 IR generator (Multiossigen SpA, Gorle, Bergamo, Italy). Under sterile conditions, the medical O_2-O_3 mixture was injected at 2 cm laterally from spinous processes in the paravertebral muscles, making sure not to be inside a blood vessel.

Measurements

The primary outcome was improvement in functional disability assessed using the ODI. It consists of 10 items on the pain and the daily function. The score of

each item is rated on a 6-point scale (0-5). The sum of the scores is expressed as a percentage of the maximum score, between 0 (none disability) and 100 (maximum disability) (26).

The secondary outcomes were reduction of pain, improvement of the quality of life, and number of days of receiving adjuvant opioid analgesic therapy. Reduction of pain was assessed using the NRS-11, a measurement scale in which the person indicates the intensity of your pain in an interval between 0 and 10, corresponding respectively to "no pain" and "worst pain imaginable" (27).

Improvement of the quality of life was assessed using the 12-item Short-Form Health Survey (SF-12), an abbreviated version of the 36-item Short-Form Survey, one of the most widely used patient-reported health outcome rating scales. The SF-12 has demonstrated construct validity, good internal consistency reliability, and responsiveness in patients with back pain. Two subscales are derived from the SF-12: the 12-item Physical Component Summary (PCS-12) score and the 12-item Mental Component Summary (MCS-12) score (28).

Opioid analgesic intake was noted from baseline to end of treatment (T2) using a patient self-completed daily diary.

Statistical Analysis

The descriptive statistics included mean and standard deviation for continuous variables and percentage and tables of frequencies for qualitative variables. A nonparametric approach was considered, based on the low number of patients. The Kruskall-Wallis and the Mann-Whitney U test was performed to compare the 4 treatment groups at the 3 times (i.e., T0, T1, T2). The significance of the change in each group at all follow-up times was determined by nonparametric Friedman and Wilcoxon signed-rank tests. The analysis was planned according to the intention-to-treat principle. All tests were 2-tailed with a level of significance of $P < 0.05$. IBM SPSS Statistics, Version 28.0.1.1 (IBM Corporation, Armonk, NY) was used for the statistical analyses.

Results

Between April 2021 and March 2022, 78 patients with acute lumbosacral radiculopathy were evaluated at the Physical Medicine and Rehabilitation Unit of Sant'Andrea Hospital, Rome, Italy. Of the 64 eligible patients, 62 agreed to participate, while 2 refused because they did not want to take part in the research. The reasons for a patient's ineligibility were as follows: pain lasting > 3 months (5 patients), NRS-11 intensity pain < 6 (4 patients), patients > 75 years of age (2 patients), lumbar spinal stenosis (2 patients), and severe motor neurological deficit (1 patient).

Of the 62 who wanted to participate, 16 patients were enrolled in group A, 15 patients in group B, 15 patients in group C, and 16 patients in group D. In group A, 15 were evaluated at T1 and T2, because 1 patient dropped out between T0 and T1. In groups B and C, 15 patients were evaluated at T1 and T2. In group D, 16 patients were evaluated at T1 and T2. The Consort Flow Diagram is shown in Fig. 1.

Patients' demographic, clinicopathologic characteristics, and primary and secondary outcomes at baseline are summarized in Table 1. In each group, disc herniation occurred more frequently at the L5-S1 level, followed by L4-L5. The percentages found are in accordance with the literature, in which approximately 95% of disc herniations in the lumbar area occur at L4-L5 or L5-S1. No significant intergroup differences ($P > 0.05$) were found at baseline assessment, except for MCS-12 in which a significant difference was found between groups ($P = 0.013$), as shown in Table 1. Specifically, a significant difference was found in the MCS-12 score between groups A and D ($P = 0.004$), groups B and D ($P = 0.023$), and groups C and D ($P = 0.01$), as shown in Table 2.

At the T2 evaluation time between groups for the

Table 2. *Mean difference between groups at 2 weeks after treatment begins (T1) and at the end of treatment (T2).*

NRS-11, mean (SD)		T0	T1	T2
Group A		8.44 (0.96)	5.47 (1.77)	4.73 (2.05)
Group B		8.53 (1.46)	4.07 (2.37)	2.73 (2.22)
Group C		8.33 (1.29)	4.67 (0.9)	2.27 (1.48)
Group D		8.31 (1.35)	3.81 (1.51)	2.13 (1.59)
P value	A vs B	0.806	0.147	0.017*
	A vs C	0.697	0.177	0.002*
	A vs D	0.984	0.011*	< 0.001*
	B vs C	0.650	0.687	0.597
	B vs D	0.569	0.575	0.420
	C vs D	0.967	0.055	0.726
ODI. mean (SD)		T0	T1	T2
Group A		53.54 (13.06)	31.92 (8.71)	26.53 (14.94)
Group B		55.62 (16.73)	19.46 (11.65)	10.95 (8.91)
Group C		56.35 (11.97)	22.23 (11.97)	8.46 (7.49)
Group D		57.62 (16.38)	14.89 (11.18)	6.76 (8.93)

Table 2 con't. *Mean difference between groups at 2 weeks after treatment begins (T1) and at the end of treatment (T2).*

P value	A vs B	0.621	0.005*	0.004*
	A vs C	0.736	0.024*	< 0.001*
	A vs D	0.450	< 0.001*	< 0.001*
	B vs C	0.709	0.708	0.370
	B vs D	0.859	0.373	0.074
	C vs D	0.766	0.078	0.369
PCS-12, mean (SD)		T0	T1	T2
Group A		28.15 (5.27)	35.71 (6.19)	38.08 (8.25)
Group B		27.25 (6.02)	40.95 (8.07)	47.38 (6.62)
Group C		27.63 (4.85)	38.72 (7.51)	49.57 (6.96)
Group D		28.75 (4.02)	46.64 (8.05)	49.74 (6.37)
P value	A vs B	0.752	0.049*	0.003*
	A vs C	0.828	0.290	0.002*
	A vs D	0.651	0.003*	< 0.001*
	B vs C	0.852	0.372	0.184
	B vs D	0.277	0.033*	0.268
	C vs D	0.663	0.013*	1.000
MCS-12, mean (SD)		T0	T1	T2
Group A		45.29 (11.47)	48.29 (10.61)	51.75 (9.85)
Group B		42.5 (9.05)	50.05 (7.95)	52.42 (6.88)
Group C		43.5 (10.21)	53.35 (9.43)	54.76 (9.05)
Group D		35.22 (5.99)	50.91 (5.45)	53.22 (11.46)
P value	A vs B	0.406	0.493	0.787
	A vs C	0.859	0.036*	0.158
	A vs D	0.004*	0.304	0.333
	B vs C	0.575	0.085	0.106
	B vs D	0.023*	1.000	0.286
	C vs D	0.01*	0.048*	0.984

Abbreviations: NRS-11, Numeric Rating Scale; ODI, Oswestry Disability Index; PCS-12, 12-item Physical Component Summary Score; MCS-12, 12-item Mental Component Summary Score; SD, standard deviation; T0, baseline; T1, 2 weeks after treatment begins; T2, end of treatment.
*Statistical significance, $P < 0.05$.

Mann-Whitney U test, a statistically significant difference was found: in the ODI between groups B and A ($P = 0.004$), groups C and A ($P < 0.001$), and groups D and A ($P < 0.001$); in the NRS-11 between groups B and A ($P = 0.017$), groups C and A ($P = 0.002$), and groups D and A ($P < 0.001$); in the PCS-12 score between group B and A ($P = 0.003$), groups C and A ($P = 0.002$), and groups D and A ($P < 0.001$); while no significant differences between groups were observed in MCS-12 score (Table 2).

At the T1 evaluation time between groups for the Mann-Whitney U test, a statistically significant difference was found: in the NRS-11 between groups D and A ($P = 0.011$); in the ODI between groups B and A ($P = 0.005$), groups C and A ($P = 0.024$), and groups D and A ($P < 0.001$); in the PCS-12 between groups B and A ($P = 0.049$), groups D and A ($P = 0.003$), and groups B and D ($P = 0.033$), and groups C and D ($P = 0.013$); in the MCS-12 between groups C and A ($P = 0.036$), groups C and D ($P = 0.048$) (Table 2).

At the Wilcoxon signed-rank test, in each group was observed a statistically significant difference for all measures at T0 vs T2. In group A was observed a significant difference in the NRS-11 ($P < 0.001$), in ODI ($P = 0.001$), among the PCS-12 ($P < 0.001$) and the MCS-12 ($P = 0.020$); in group B, in the NRS-11 ($P < 0.001$), in the ODI ($P < 0.001$), among the PCS-12 ($P < 0.001$) and the MCS-12 ($P = 0.001$); in group C, in the NRS-11 ($P < 0.001$), in the ODI ($P < 0.001$), among the PCS-12 ($P < 0.001$) and the MCS-12 ($P = 0.002$); in group D in the NRS-11 ($P < 0.001$), in the ODI ($P < 0.001$), among the PCS-12 ($P < 0.001$) and the MCS-12 ($P = 0.004$) (Table 3).

The average days of opioid usage were similar in the 4 treatment groups (8.33 in group A, 8.33 in group B, 8.33 in group C, and 8.75 in group D). However, the percentage of patients requiring adjuvant opioid therapy differed remarkably between groups: 60% in group A, 40% in group B, 20% in group C, and 25% in group D (Table 4).

Discussion

Acute lumbosacral radiculopathy is a debilitating condition causing LBP radiating in a dermatomal pattern, and sensory and motor loss depending on the severity of nerve compression. It involves an increased risk of pain-related disability, functional limitations, and negative effects on physical as well as mental health, thus leading to high costs for the health care system and society (1). In the management of lumbar-radiating pain, drugs commonly prescribed include NSAIDs, skeletal muscle relaxants, systemic corticosteroids, antidepressants, and anticonvulsants. However, the efficacy and tolerability of commonly prescribed analgesic and adjuvant drugs has not been well established and there are no general recommendations and clear guidelines (4,6). Despite the lack of clinical evidence, the use of systemic corticosteroids for acute lumbosacral radiculopathy remains relatively common, helping to reduce swelling and related compression on the affected nerve, and relieving radicular pain symptoms (6).

The main objective of this prospective study was

to examine the difference between pharmacological therapy alone (group A) and a multimodal treatment (groups B, C, D) in patients affected by acute lumbosacral radiculopathy. Although statistically significant improvements were found at the end of treatment (T2) for all measures in each group, the multiple treatment groups improved significantly more. Our results show a statistically significant difference in functional disability between the group that received pharmacological therapy alone and other study groups, confirming the hypothesis that the multimodal approach, combining the neurotrophic/antinociceptive nutraceutical composed and/or O_2-O_3 therapy with pharmacological therapy, would lead to greater improvement in functional disabilities. Among the secondary outcome measures, we observed an improvement in perceived pain and in the physical component of the quality of life in patients treated with multimodal therapy compared to the pharmacological therapy group, while no significant differences between groups were observed in the mental health area of quality of life. In group D, by combining all treatment, significant differences were already observed at the T1 evaluation time compared to group A.

A further objective of the study was to describe the opioid analgesics consumption trends in the 4 treatment groups. In group A, study results show a much higher proportion of patients requiring adjuvant opioid therapy to optimize pain control compared to other study groups. While the groups that received O_2-O_3 therapy (groups C and D), show a lower percentage.

In this prospective study, a nutraceutical supplement of 800 mg/daily of ALA + 600 mg/daily of PEA + 200 mg/daily myrrh was orally administered. ALA is a compound commonly located in the mitochondria, where it acts as a cofactor for some enzymatic complexes involved in cellular energy metabolism, such as pyruvate dehydrogenase and α-ketoglutarate dehydrogenase (29). ALA is also widely known for its antioxidant properties; it not only improves but also restores the intrinsic antioxidant systems (30). It inactivates free radicals, and the reduced form can reduce the oxidized forms of other antioxidant agents, including glutathione, and vitamins C and E, having a determinant role in oxidative metabolism (30). Moreover, ALA has many biochemical anti-inflammatory properties involved in modulation of signal transduction pathways, like insulin, nuclear factor kappa B, and adenosine monophosphate protein kinase pathways (29). Its antioxidant and free radical scavenging properties, and its anti-inflammatory properties have been recognized as part of the mechanism underlying the clinical benefits observed in treatment of some neuropathic pain and peripheral nerve injuries (12-16). Preclinical studies (31-33) demonstrate protective effects of ALA on experimental sciatic nerve crush injury models, promoting peripheral nerve regeneration via its anti-inflammatory and antiapoptotic effects; while clinical evidence (34-35) suggests positive properties of thioctic acid in patients with compressive radiculopathy

Table 3. *Mean difference within groups at 2 weeks after treatment begins (T1) and at the end of treatment (T2).*

	T0-T1	T1-T2	T0-T2
NRS-11			
Group A	< 0.001*	0.042*	< 0.001*
Group B	< 0.001*	0.020*	< 0.001*
Group C	< 0.001*	< 0.001*	< 0.001*
Group D	< 0.001*	0.002*	< 0.001*
ODI			
Group A	< 0.001*	0.026*	0.001*
Group B	< 0.001*	0.011*	< 0.001*
Group C	< 0.001*	0.002*	< 0.001*
Group D	< 0.001*	0.001*	< 0.001*
PCS-12			
Group A	< 0.001*	0.031*	< 0.001*
Group B	< 0.001*	0.008*	< 0.001*
Group C	< 0.001*	0.002*	< 0.001*
Group D	< 0.001*	0.075	< 0.001*
MCS-12			
Group A	0.221	0.071	0.020*
Group B	0.002*	0.099	0.001*
Group C	0.009*	0.279	0.002*
Group D	< 0.001*	0.158	0.004*

Abbreviations: NRS-11, Numeric Rating Scale; ODI, Oswestry Disability Index; PCS-12, 12-item Physical Component Summary Score; MCS-12, 12-item Mental Component Summary Score; T0, baseline; T1, 2 weeks after treatment begins; T2, end of treatment.
*Statistical significance, $P < 0.05$.

Table 4. *Opioid analgesics consumption.*

Opioid Drug	n (%)	Days (mean, SE)
Group A (n = 15)	9 (60%)	8.33 (1.155)
Group B (n = 15)	6 (40%)	8.33 (1.308)
Group C (n = 15)	3 (20%)	8.33 (1.667)
Group D (n = 16)	4 (25%)	875 (2.394)

Abbreviations: n, number; SE, standard error.

syndrome from disc-nerve root conflict, improving nerve conduction and reducing pain, numbness, and paresthesia. In a recent multicentric observational prospective study (36), a subgroup of 312 patients with chronic LBP and sciatica was treated with a combination of neurotrophic agents containing ALA and after a 2-month follow-up was observed an improvement in both perceived pain and functional disabilities. In our study, the nutraceutical supplementation acts in patients suffering from acute lumbosacral radiculopathy as short-term adjuvant therapy of the pharmacological therapy, showing an improvement of clinical outcome measures as early as 4 weeks from the baseline. Beyond as well as the known neurotrophic and antinociceptive potentialities of ALA, myrrh and PEA act as biological modulators, favoring the physiological tissue response. PEA is an endocannabinoid-like bioactive lipid mediator, belonging to the N-acyl-ethanolamine fatty acid amide family (37). It is widely recognized to promote the resolution of neuroinflammation and exert neuroprotection (17-20). In a recent post hoc analysis (38) of a controlled study in patients with LBP-sciatica, the PEA was extremely effective on pain and function, exerting a predominant action on the neuropathic pain component. PEA is currently available in different formulations and a debate is open on the micronization of PEA, in particular, the advantages (or lack thereof) of micronized PEA over unmicronized PEA. The process of micronization may lead to a better adsorption of the drug molecules; however, in literature there is only a report (39) in which micronized/ultramicronized PEA are more efficacious than unmicronized PEA in an experimental rat model of inflammatory pain. Direct comparisons of the different formulations of PEA in humans are lacking, and thus there is no clinical data yet to support the use of one formulation over another.

Lastly, the analgesic properties of myrrh (an extract of Commiphora myrrha) have been known since ancient times and depend on the high content of bioactive furanodienes (40). A direct comparison with some of the most frequently used drugs (e.g., diclofenac, ketoprofen, ibuprofen, paracetamol, tramadol, and ketorolac) revealed that myrrh has similar effects, although it required a longer course of treatment (i.e., 20 days) (40).

In this study, O_2-O_3 therapy was used for its analgesic, antioxidant, anti-inflammatory, and immunomodulating properties in conjunction with pharmacological therapy or with pharmacological therapy and nutraceutical supplements. Over the years, several studies evaluated by Magalhaes et al (22) in a systematic review have demonstrated the utility of intramuscular paravertebral O_2-O_3 therapy, showing a level of evidence of II-1 in the treatment of back pain secondary to herniated disc with a grade of recommendation 1B. O_2-O_3 therapeutic effects are obtained by amelioration of tissue oxygenation in the proximity of the nerve root, inhibiting inflammatory mediators, reducing the synthesis of prostaglandins, and decreasing oxidative stress through an increase of endogenous antioxidant pathways (22,41,42).

Among neuropathic mechanisms of lumbosacral radiculopathy, the reactive oxygen species-triggered inflammatory process, which develop after the peripheral neuropathic lesion is acknowledged as a relevant factor responsible for neuropathic pain, leading to pain and loss of nerve conduction functionality. In such a way, the ozone could represent a suitable strategy, promoting the antioxidant-prooxidant balance and the concomitant preservation of the cell redox state.

Beyond the neuropathic mechanisms, understanding and identifying sources of potential nociceptive sensitization (both peripheral and central) that contribute to acute painful lumbosacral radiculopathy may help guide a rational approach to analgesia. Several subsets or combinations of tissue changes may be involved, including acute herniated disc, acute annular tear, and herniated disc fragments, triggering the development of edema, and local cellular abnormalities. An increased synthesis of pro-inflammatory cytokines in the spinal cord leads to the expression of multiple algesic mediators and heightened nociceptive activity, while macrophages and peripheral T cells cross the blood-brain barrier into the parenchyma of the spinal cord, causing further increased neuroimmune activation and peripheral sensitization (43-45). Even the nerve root injury or compression is associated with release of inflammatory mediators that sensitize peripheral nociceptors. The peripheral sensitization manifests as primary allodynia (i.e., sensation arising from an innocuous stimulus) and primary hyperalgesia (i.e., sensation arising from a noxious stimulus) (46). These peripheral sensitization processes also contribute to the development of central sensitization and maintenance of pain in the days to weeks after an acute lumbosacral pain episode, by an amplification of synaptic strength in nociceptive circuits (47). Alterations in pain processing, both peripherally and centrally, affect the ultimate perception of pain. Together with the complexity of the nervous system and pain modulation mechanisms,

psychological aspects (e.g., depression, anxiety, pain catastrophizing) likely interact with functional connectivity in pain-relevant higher brain centers that could magnify incoming nociceptive signals (48). The presence of these negative constructs and affective states can be a consequence of the acute painful experience and may influence recovery and disease prognosis, playing a critical role in the evolution from acute to chronic pain (49-51).

The early approach proposed in our study with a combination of agents targeting nociceptive and neuropathic pain mechanisms (e.g., multimodal analgesia), dampening, or reducing these areas of sensitization, could positively impact the pain trajectory and recovery in patients with acute painful lumbosacral radiculopathy, and potentially prevent the development of chronic pain. Pharmacological therapy forms the mainstay of our treatment. Corticosteroids target nociceptive pain, as inflammation is a prominent cause of nociception. The effects of corticosteroids in acute lumbosacral radiculopathy are related to their anti-inflammatory effects, which may help reduce the local release of inflammatory cytokines, swelling, and related compression on the affected nerve (52). Opioids, used as adjuvant analgesics, target both nociceptive and to a lesser extent neuropathic pain, and their analgesic efficacy in the short-term management of acute pain states is well established. O_2-O_3 therapy and nutraceutical supplements have been used as complementary therapies for pain management.

On the base of these considerations and considering the good tolerability of the treatments, our study supports a multimodal approach, including pharmacological, neurotrophic, and O_2-O_3 treatments, with considerable attention for ALA, that has the higher degree of evidence among neurotrophic agents in neuropathic pain.

Nutraceutical supplements of ALA, PEA, myrrh, and O_2-O_3 therapy may be a useful choice in the multitherapeutic strategy for acute lumbosacral radiculopathy, since they can contribute to pain control due to their prevalently anti-inflammatory, antioxidant, and neuroprotection action.

The comparison of several different approaches vs pharmacological therapy alone can be considered one of the strengths of this study. To the best of our knowledge, at the time of this research, no study has compared simultaneously these multimodal treatments in pain management of acute lumbosacral radiculopathy.

Limitation

Limitations of our study may be represented by the small sample size, which reduced the possibility of extrapolating the results to other patient populations, the long-term outcomes were not assessed, and the lack of a control group that included conservative management, such as physical therapy, NSAIDs, or acetaminophen. Therefore, the authors recommend performing high-quality clinical trials with a larger sample size. Also, comparing the efficacy of our proposed treatments with first-line treatments could be a matter of future research. Lastly, successfully treated patients should be followed-up to determine whether the outcome was sustained.

Conclusions

Treatment of acute LBP with or without lower extremity pain is a major concern. The current study supports a multimodal approach combining nutraceutical supplements and O_2-O_3 therapy with pharmacological therapy in the treatment of acute painful lumbosacral radiculopathy secondary to disc herniation. The combination of neurotrophic and antioxidant therapies represents an etiopathogenetic approach, not purely symptomatic, that reduces symptomatology and avoids progression of the nerve damage.

References

1. Urits I, Burshtein A, Sharma M, et al. Low back pain, a comprehensive review: Pathophysiology, diagnosis, and treatment. *Curr Pain Headache Rep* 2019; 23:23.
2. Nicol AL, Adams MCB, Gordon DB, et al. AAAPT diagnostic criteria for acute low back pain with and without lower extremity pain. *Pain Med* 2020; 21:2661-2675.
3. Berry JA, Elia C, Saini HS, Miulli DE. A review of lumbar radiculopathy, diagnosis, and treatment. *Cureus* 2019; 11:e5934.
4. Bailly F, Trouvin AP, Bercier S, et al. Clinical guidelines and care pathway for management of low back pain with or without radicular pain. *Joint Bone Spine* 2021; 88:105227.
5. Khorami AK, Oliveira CB, Maher CG, et al. Recommendations for diagnosis and treatment of lumbosacral radicular pain: A systematic review of clinical practice guidelines. *J Clin Med* 2021; 10:2482.
6. Oros M, Oros Jar M, Grabar V. Steroids and L-lysine aescinate for acute radiculopathy due to a herniated lumbar disk. *Medicina (Kaunas)* 2019; 55:736.
7. Mallet ML, Hadjivassiliou M, Sarrigiannis PG, Zis P. The role of oxidative stress in peripheral neuropathy. *J Mol Neurosci* 2020;

70:1009-1017.

8. Schwartz ES, Kim HY, Wang J, et al. Persistent pain is dependent on spinal mitochondrial antioxidant levels. *J Neurosci* 2009; 29:159-168.
9. Ranieri M, Sciuscio M, Cortese AM, et al. Possible role of alpha-lipoic acid in the treatment of peripheral nerve injuries. *J Brachial PlexPeripher Nerve Injury* 2010; 5:15.
10. Petersen Shay K, Moreau RF, Smith EJ, Hagen TM. Is alpha-lipoic acid a scavenger of reactive oxygen species in vivo? Evidence for its initiation of stress signaling pathways that promote endogenous antioxidant capacity. *IUBMB Life* 2008; 60:362-367.
11. Gomes MB, Negrato CA. Alpha-Lipoic acid as a pleiotropic compound with potential therapeutic use in diabetes and other chronic diseases. *Diabetol Metab Syndr* 2014; 6:80.
12. Mrakic-Sposta S, Vezzoli A, Maderna L, et al. R(+)-Thioctic acid effects on oxidative stress and peripheral neuropathy in type II diabetic patients: Preliminary results by electron paramagnetic resonance and electroneurography. *Oxid Med Cell Longev* 2018; 2018:1767265.
13. Karalis DT, Karalis T, Karalis S, Kleisiari AS, Malakoudi F, Maimari KEV. The effect of alpha-lipoic acid on diabetic peripheral neuropathy and the upcoming depressive disorders of type II diabetics. *Cureus* 2021; 13:e12773.
14. Nádró B, Lőrincz H, Molnár Á, et al. Effects of alpha-lipoic acid treatment on serum progranulin levels and inflammatory markers in diabetic neuropathy. *J Int Med Res* 2021; 49:3000605211012213.
15. Pacini A, Tomassoni D, Trallori E, et al. Comparative assessment of the activity of racemic and dextrorotatory forms of thioctic (alpha-lipoic) acid in low back pain: Preclinical results and clinical evidences from an open randomized trial. *Front Pharmacol* 2021; 12:607572.
16. Passiatore M, Perna A, De-Vitis R, Taccardo G. The use of alfa-lipoic acid-R (ALA-R) in Patients with mild-moderate carpal tunnel syndrome: A randomised controlled open label prospective study. *Malays Orthop J* 2020; 14:1-6.
17. Rankin L, Fowler CJ. The basal pharmacology of palmitoylethanolamide. *Int J Mol Sci* 2020; 21:7942.
18. Clayton P, Subah S, Venkatesh R, Hill M, Bogoda N. Palmitoylethanolamide: A potential alternative to cannabidiol. *J Diet Suppl* 2021; 20:1-26.
19. Skaper SD, Facci L, Fusco M, et al. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. *Inflammopharmacology* 2014; 22:79-94.
20. D'Amico R, Impellizzeri D, Cuzzocrea S, Di Paola R. ALIAmides update: Palmitoylethanolamide and its formulations on management of peripheral neuropathic pain. *Int J Mol Sci* 2020; 21:5330.
21. De Sire A, Agostini F, Lippi L, et al. Oxygen-Ozone therapy in the rehabilitation field: State of the art on mechanisms of action, safety and effectiveness in patients with musculoskeletal disorders. *Biomolecules* 2021; 11:356.
22. Magalhaes F, Dotta L, Sasse A, Teixera M, Fonoff E. 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-E129.
23. Bocci V, Borrelli E, Zanardi I, Valter Travagli V. The usefulness of ozone treatment in spinal pain. *Drug Des Devel Ther* 2015; 9:2677-2685.
24. Human D. Declaration of Helsinki. *Lancet* 2001; 236:357.
25. Brzeziński K, Wordliczek J. Comparison of the efficacy of dexketoprofen and diclofenac in treatment of non-specific low back pain. *Ann Agric Environ Med* 2013; 1:52-56.
26. Fairbank JC, Pynsent PB. The Oswestry Disability Index. *Spine (Phila Pa1976)* 2000; 25:2940-2952.
27. 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.
28. 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.
29. Salehi B, Berkay Yılmaz Y, Antika G, et al. Insights on the use of α-lipoic acid for therapeutic purposes. *Biomolecules* 2019; 9:356.
30. Moura FA, de Andrade KQ, dos Santos JC, Goulart MO. Lipoic acid: Its antioxidant and anti-inflammatory role and clinical applications. *Curr Topics Med Chem* 2015; 15:458-483.
31. Horasanli B, Hasturk AE, Arikan M, et al. Comparative evaluation of the electrophysiological, functional and ultrastructural effects of alpha lipoic acid and cyanocobalamin administration in a rat model of sciatic nerve injury. *J Back Musculoskelet Rehabil* 2017; 30:967-974.
32. Kurt Oktay KN, Akpinar P, Unlu Ozkan F, Aktas I, Ersoy Canillioglu Y, Erkanli Senturk G. The effect of alpha lipoic acid on the recovery of sciatic nerve injury in rats: A prospective randomized controlled trial. *Am J Phys Med Rehabil* 2021; 100:780-789.
33. Kocaoğlu S, Aktaş Ö, Zengi O, Tufan A, Karagöz Güzey F. Effects of alpha lipoic acid on motor function and antioxidant enzyme activity of nerve tissue after sciatic nerve crush injury in rats. *Turk Neurosurg* 2017. [Epub ahead of print]
34. Memeo A, Loiero M. Thioctic acid and acetyl-L-carnitine in the treatment of sciatic pain caused by a herniated disc: A randomized, double-blind, comparative study. *Clin Drug Investig* 2008; 28:495-500.
35. Ranieri M, Sciuscio M, Cortese AM, et al. The use of alpha-lipoic acid (ALA), gamma linolenic acid (GLA) and rehabilitation in the treatment of back pain: Effect on health-related quality of life. *Int J Immunopathol Pharmacol* 2009; 22(suppl 3):45-50.
36. Checchia GA, Letizia Mauro G, Morico G, et al. Management of peripheral neuropathiesstudy group. Observational multicentric study on chronic sciatic pain: Clinical data from 44 Italian centers. *Eur Rev Med Pharmacol Sci* 2017; 21:1653-1664.
37. Clayton P, Hill M, Bogoda N, Subah S, Venkatesh R. Palmitoylethanolamide: A natural compound for health management. *Int J Mol Sci* 2021; 22:5305.
38. Cruccu G, Stefano GD, Marchettini P, Truini A. micronized palmitoylethanolamide: A post hoc analysis of a controlled study in patients with low back pain - sciatica. *CNS Neurol Disord Drug Targets* 2019; 18:491-495.
39. Impellizzeri D, Bruschetta G, Cordaro M, et al. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. *J Neuroinflammation* 2014; 11:136.
40. Germano A, Occhipinti A, Barbero F, Maffei ME. A pilot study on bioactive constituents and analgesic effects of MyrLiq®, a commiphora myrrha extract with a high furanodiene content. *Biomed Res Int* 2017; c2017:3804356.
41. Valdenassi L, Franzini M, Simonetti V, Ricevuti G. Oxygen-Ozone therapy:

Paradoxical stimulation of ozone. *Ozone Ther* 2016; 1:2-4.

42. Latini E, Curci ER, Nusca SM, et al. Medical ozone therapy in facet joint syndrome: An overview of sonoanatomy, ultrasound-guided injection techniques and potential mechanism of action. *Med Gas Res* 2021; 11:145-151.
43. Shamji MF, Setton LA, Jarvis W, et al. Proinflammatory cytokine expression profile in degenerated and herniated human intervertebral disc tissues. *Arthritis Rheum* 2010; 62:1974-1982.
44. Cosamalón-Gan I, Cosamalón-Gan T, Mattos-Piaggio G, Villar-Suárez V, García-Cosamalón J, Vega-Álvarez JA. Inflammation in the intervertebral disc herniation. *Neurocirugia (Astur: Engl Ed)* 2021; 32:21-35.
45. Brisby H. Pathology and possible mechanisms of nervous system response to disc degeneration. *J Bone Joint Surg Am* 2006; 88 (suppl 2):68-71.
46. Defrin R, Devor M, Brill S. Tactile allodynia in patients with lumbar radicular pain (sciatica). *Pain* 2014; 155:2551-2559.
47. Huang Y, Li Y, Zhong X, et al. Src-Family kinases activation in spinal microglia contributes to central sensitization and chronic pain after lumbar disc herniation. *Mol Pain* 2017; 13:1744806917733637.
48. Zhang SS, Wu W, Yang JM, Wang CH. Abnormal spontaneous brain activity in acute low-back pain revealed by resting-state functional MRI. *Am J Phys Med Rehabil* 2017; 96:253-259.
49. Swinkels-Meewisse IEJ, Roelofs J, Oostendorp RAB, Verbeek ALM, Vlaeyen JWS. Acute low back pain: Pain-Related fear and pain catastrophizing influence physical performance and perceived disability. *Pain 2006*; 120:36-43.
50. Lanier DC, Stockton P. Clinical predictors of outcome of acute episodes of low back pain. *J Fam Pract* 1988; 27:483-489.
51. Thomas JS, France CR. Pain-Related fear is associated with avoidance of spinal motion during recovery from low back pain. *Spine (Phila Pa 1976)* 2007; 32:E460-E466.
52. Goldberg H, Firtch W, Tyburski M, et al. Oral steroids for acute radiculopathy due to a herniated lumbar disk: A randomized clinical trial. *JAMA* 2015; 313:1915-1923.