Low back pain (LBP) is one of the most common and important clinical, social, economic, and public health problems affecting the human population worldwide (1). Around 70% of adults suffer from LBP at some point in their lifetime with various degrees of symptom severity. Additionally, 1.6% to 43% of these patients have LBP associated with sciatic symptoms (2). In the United States, the incidence of chronic low back pain ranges from 15% to 45%, with a prevalence of 30% (1). Most back pain has no recognizable cause...
on imaging studies and is usually attributed to muscle strain or ligament injuries (65%-70%). In 5% to 15% of cases, the source of LBP is related to degenerative joints and disc disease (3). The natural history of disk herniation is favorable; improvement of symptoms is the norm, and most episodes resolve spontaneously or after conservative therapy. However, studies have shown that low back pain is sometimes still present after long periods of time (at least 12 months) in 37% to 54% of patients (1,2).

Besides oral pharmacological and rehabilitation treatments, ozone therapy has emerged as an alternative or additional treatment option for these patients, particularly in Europe (4,5). Despite its widespread use to treat a variety of conditions, ozone therapy remains unknown to most physicians. Ozone (O3) is an allotropic form of oxygen, primarily known for its ecological properties, industrial application and therapeutic effects. Questions persist concerning its potential toxicity as an oxidant agent versus its reported clinical efficacy. Several mechanisms of action have been proposed to explain the efficacy of ozone therapy including analgesic, anti-inflammatory and oxidant action on proteoglycans (e.g., in the nucleus pulposus). Ozone is administered in the form of an oxygen-ozone gas mixture at nontoxic concentrations ranging from 1 to 40 µg of ozone per mL of oxygen, using various percutaneous methods (5).

Percutaneous techniques minimize the invasive nature of surgery, rendering administration more straightforward and faster while sparing healthy tissue and avoiding or minimizing complications such as postsurgical infection (6). Those techniques have been applied as an adjunct treatment for LBP and used in association with ozone injections have yielded good results (4). However, the effectiveness of ozone injections for the treatment of LBP remains a matter of debate. In order to investigate the effectiveness and safety of ozone therapy for this specific purpose, the authors performed a systematic review and meta-analysis of the literature, focusing on observational studies and randomized controlled trials (RCTs) in patients with subacute or chronic LBP.

1.0 Methodology

The methodology utilized in this work follows the systematic review process derived from evidence-based systematic review and meta-analysis of randomized trials (7) and the PRISMA statement (8).

1.1 Inclusion Criteria

1.1.1 Types of Studies

Three review authors screened the abstracts of studies in all languages against the inclusion criteria. They then retrieved all possibly relevant articles in full text for comprehensive assessment of the quality and satisfaction of inclusion criteria.

The review focused on randomized trials, systematic reviews, observational studies, and reports of complications. All studies providing appropriate management with outcome evaluations at 6 months or longer and statistical evaluations were reviewed. Reports without appropriate diagnosis, nonsystematic reviews, book chapters, and case series with fewer than 10 patients were excluded from the initial search in the databases.

1.1.2 Types of Participants

Participants were adults aged at least 18 years with low back pain due to lumbar disc herniation or degenerative disc disease treated by the interventional procedures 2.1.3 below.

1.1.3 Types of Interventions

Interventions were injections of an oxygen-ozone mixture associated or compared with steroids, and local anesthetic applied to intradiscal, intramuscular paraspinal, juxtaforaminal, periganglionic or epidural, guided by fluoroscopy or tomography.

1.1.4 Types of Outcome Measures

The primary outcome measure was pain relief (short term < 6 months and long-term > 6 months) in accordance with Staal et al (9).

1.2 Review criteria

The search in the databases was performed independently by 3 authors who selected the articles for analysis. Each study was evaluated by 3 physicians for stated criteria and any disagreement was resolved by a fourth physician. The other author was responsible for statistical analysis.

1.3 Adverse Events or Side Effects

Adverse effects and complications were analyzed according to the description of the authors or based on case reports.

1.4 Search Methods for Study Identification

Searches were performed from the following sources:
Ozone Therapy for Low Back Pain

1. PubMed from 1966
2. EMBASE from 1980
   www.embase.com/
3. Cochrane Library
   www.thecochranelibrary.com/view/0/index.html
4. DARE and HTA
   Search period included from 1966 through September 2011.

1.4.1 Search Strategy
The search terminology included the terms ozone-therapy, ozone, ozone therapy, chronic low back pain, back pain, pain, failed back surgery syndrome and ozonucleolysis.

At least 3 of the review authors independently, in a standardized manner, performed each search. Accuracy was confirmed by a statistician. All searches were combined to obtain a unified search strategy. Any disagreements between reviewers were resolved by a third author and consensus.

1.4.2 Assessment of Methodological Quality
The methodological quality assessment was performed by 3 reviewers and any discrepancies were evaluated by a fourth reviewer and consensus was reached.

The quality of each individual article included in this analysis was assessed by modified Cochrane review criteria with weighted scores (10) for randomized trials and the Agency for Healthcare Research and Quality (AHRQ) quality criteria for assessment of observational studies (11). Only the observational studies scoring at least 50 on weighted scoring criteria were included for analysis. Methodological quality assessment criteria are described in Tables 1 and 2.

1.5 Data Extraction and Management
Three review authors independently extracted the data from the included studies. Disagreements were resolved by discussion among the 3 review authors; if no agreement could be reached, it was planned a fourth author would decide.

1.6 Measurement of Treatment Effect and Data Synthesis (Meta-analysis)
The authors used a standardized data extraction form for independent inclusion of the study population, intervention, study design, and outcome measures for randomized controlled trials. The meta-analysis was performed using the Review Manager 5.0 (The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark) with the random-effect model. Dichotomous data were compared using odds ratio (OR). Respective 95% confidence intervals (CI) were calculated for each estimate and presented in forest plots. The pooled OR, symbolized by a solid diamond at the bottom of the forest plot (the width of which represents the 95% CI), is the best estimate of the true (pooled) outcome. The effect of the treatment was expressed as a ratio of the ozone therapy arm over the control arm.

1.7 Analysis of Evidence
Analysis was conducted using 5 levels of evidence, ranging from Level I to III with 3 subcategories in level II, as illustrated in Table 1(12).

1.8 Recommendations
Grading recommendations were based on the criteria stated by Guyatt et al (13) as illustrated in Table 2.

1.9 Outcomes of the Studies
A study was judged positive if the ozone injections were clinically relevant and effective. Regarding randomized studies, this indicates that the difference in the effect for the primary outcome measure was statistically significant on the conventional 5% level. In a negative study, no difference between the studied group and the controls or no improvement from baseline was reported (9).

Table 1. Levels of evidence based on the Quality data available in the literature (USPSTF).

<table>
<thead>
<tr>
<th>I:</th>
<th>Evidence obtained from multiple properly conducted diagnostic accuracy studies.</th>
</tr>
</thead>
<tbody>
<tr>
<td>II-1:</td>
<td>Evidence obtained from at least one properly conducted diagnostic accuracy study of adequate size.</td>
</tr>
<tr>
<td>II-2:</td>
<td>Evidence obtained from at least one properly designed small diagnostic accuracy study.</td>
</tr>
<tr>
<td>II-3:</td>
<td>Evidence obtained from diagnostic studies of uncertainty.</td>
</tr>
<tr>
<td>III:</td>
<td>Opinions of respected authorities, based on clinical experience descriptive studies Evidence obtained from case reports or reports of expert committees.</td>
</tr>
</tbody>
</table>

Adapted and modified from the U.S. Preventive Services Task Force (USPSTF)(12).
2.0 Results

Our search strategy yielded multiple studies evaluating the effectiveness of ozone injected into the disc and/or periforaminal or at the paravertebral muscles. From the initial search (117 articles) only 35 were reviewed: 30 studies, including 7 randomized trials (14-20) and 23 observational studies, and 5 reports of complications (21-25) (Fig. 1).

2.1 Randomized Trials

2.1.1 Methodological Quality Assessment

From the 7 randomized trials, 4 (14-17) met the established inclusion criteria. Three of them were excluded from the meta-analysis: one utilized collagenase (19) associated with ozone and steroid; Gautam et al (20) utilized intradiscal radiofrequency with ozone, and the other due to methodological issues that would invalidate the meta-analysis (18). The results of the methodological quality assessment of randomized studies are illustrated in Table 3. The quality assessment criteria ranged from 56 to 84 points for evidence synthesis.

2.1.2 Descriptive results of randomized studies

In the randomized series of 306 patients, Bonetti et al (14) reported that 57.5% of 80 patients in the disc disease group treated with steroid deemed the clinical outcome to be excellent, as did 62.8% of 70 patients in the group with no disc disease after steroid infiltration (Table 4). Whereas in the ozone therapy group, 74.4% of 86 patients with disc disease reported complete remission of pain, as did 75.0% of 70 patients with no disc disease. In another randomized study, Gallucci et al (16) observed a satisfactory success rate with ozone-therapy combined with intraforaminal and intradiscal steroid and anesthetic injection compared to steroid alone.
Zambello et al (15) randomized 351 patients with low back pain for treatment with either ozone or steroid (epidural) and planned a crossover during the follow-up to the other group in case of failure to respond to treatment after 4 weeks of therapy. The long-term outcome remained excellent or good in 47.3% of 171 patients treated by epidural steroid injections and in 77.1% of 180 patients treated with O2-O3. Eleven patients in the ozone group were subjected to crossover to epidural steroid injections whereas 38 patients in the epidural group were submitted to crossover to the ozone group. Only 36.4% of patients in the crossover group to epidural injection presented excellent/good remission of pain while 70.8% of patients in the epidural group who were submitted to crossover to ozone therapy reported an excellent/good outcome.

Recently, Paoloni et al (17) conducted a multicenter, randomized, double-blind, “simulated therapy”-controlled clinical trial. Thirty-six patients received intramuscular-paravertebral ozone injections whereas 24 received simulated lumbar intramuscular-paravertebral injections. The simulated injection was administered us-
Table 3. Randomized trials on the efficacy of ozone therapy for low-back pain.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Criterion weight</th>
<th>Paoloni (18)/Italy/2009</th>
<th>Bonetti (15)/Italy/2005</th>
<th>Gallucci (17)/Italy/2007</th>
<th>Zambello (16)/Italy/2006</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Study population</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A Homogeneity</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>B Comparability of relevant baseline characteristics</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>C Randomization procedure adequate</td>
<td>4</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>D Drop-outs described for each study group separately</td>
<td>3</td>
<td>3</td>
<td>-</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>E &lt; 20% loss to follow-up</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>F &gt; 50 subjects in the smallest group</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G Interventions included in protocol and described</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>H Pragmatic study</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>I Co-interventions avoided</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>J Placebo-controlled</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><strong>Effect</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>K Patients blinded</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>L Outcome measures relevant</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>M Blinded outcome assessments</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>N Follow-up period adequate</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Data-presentation and analysis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>O Intention-to-treat analysis</td>
<td>5</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>P Frequencies of most important outcomes presented for each treatment group.</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td>84</td>
<td>70</td>
<td>70</td>
<td>70</td>
<td>56</td>
</tr>
</tbody>
</table>


Applying a false needle that pricked the skin without piercing it, applied at the lumbar paraspinal level, followed by hand-applied pressure on the same site designed to reproduce the load sensation commonly described after O2-O3 injections. Patients who received ozone had significant lower pain scores (mean visual analog scale [VAS] was 0.66 in the study group and 4.00 in the control group) compared to patients who received simulated therapy. Also, a greater percentage of patients became pain-free (61% versus 33%, \( P < 0.01 \)) in the ozone group. Active ozone therapy was followed by a statistically significant shorter time on nonsteroidal an-
### Table 4. Results of randomized studies of ozone therapy for low-back pain

<table>
<thead>
<tr>
<th>Author/Country/Year/Methods/Type of pain</th>
<th>Participants</th>
<th>Design of study/Intervention(s) (guided by CT or fluoroscopy)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bonetti (15), Italy, 2005, RA, DB</td>
<td>306 patients with acute or chronic low back pain and sciatic nerve pain were treated. They were divided into two groups: Group with disc disease (bulging disk, protrusion or extrusion; n=166); group with non-disc vertebral disease (osteoarthrosis, spondylolisthesis, facet joint syndrome; n=140) and received ozone or steroid infiltrations.</td>
<td>The patients were divided into two groups with their subgroups: injections were infiltrated adjacent to neural foramina or facet joint regions guided by CT. G1=Ozone (7mL-25µg/mL): With disc disease: n=86 Non-disc disease: n=70 G2= (Steroid): With disc disease:n=80 Non-disc disease: n=70</td>
<td>Timing: 1 week, 3 and 6 months. Outcome measures: (MacNab Score): Excellent: pain free and return to work Good: Pain relief 50% or more Poor: Pain relief 30% or less.</td>
<td>6 months (excellent and good)</td>
</tr>
<tr>
<td>Galluci17, Italy, 2007, RA, DB</td>
<td>159 patients with lumbar disc herniation and radicular pain. All patients complained of pain for at least 8 weeks with poor clinical improvement after conservative treatment.</td>
<td>The patients were divided into two groups: all received intradiscal and intraforaminal injections of a steroid and a local anesthetic or ozone (7mL-28µg/mL). G1(n=82) Steroid / local anesthetic G2(n=77)Steroid / local anesthetic and ozone</td>
<td>Timing: 2 weeks, 3 and 6 months; Outcome measures: Classified as successful if the Oswestry Disability Index was no greater than 20% at follow up and unsuccessful otherwise.</td>
<td>6 months Successful: G1=47% G2=74% Unsuccessful: G1=53% G2=26%</td>
</tr>
<tr>
<td>Paoloni18 , Italy, 2009, RA, DB</td>
<td>60 patients with acute low back pain and/or radiating pain of moderate to severe intensity (VAS ≥ 5) and MRI evidence of disc protrusion with or without disc degeneration in the spinal segments involved in the pain.</td>
<td>The patients were divided into two groups: G1(n=36): Ozone intramuscular paravertebral lumbar infiltrations (3/wk for 5 consecutive weeks) of ozone (20mL - 20µg/mL). G2(n=24): Simulated therapy: injection using a false needle that pricked the skin without piercing it, pressure applied at the lumbar paravertebral level.</td>
<td>Timing: 15 and 30 days, 2 weeks, 3 and 6 months. Outcome measures: (at the end of follow up) Pain free on VAS score ≤ 1, Backill questionnaire, SF-36, Kellner scores.</td>
<td>6 months Pain-free: G1=61% G2=33% Backill score: G1=+13.0 G2=+5.6 Kellner and SF-36: No differences between groups MRI findings: Unchanged Drug intake: Decreased</td>
</tr>
<tr>
<td>Zambello16, Italy, 2006, RA, DB</td>
<td>351 patients with chronic irradiating low back pain over sciatic nerve and failure to respond to medical treatment were randomly assigned to one of two groups.</td>
<td>The patients were divided into two groups: G1(n=171): Steroid at intervertebral space G2(n=180): Ozone into the paravertebral muscle, 5mL- 20µg/mL)</td>
<td>Timing: 3 weeks and 6 months; Outcome measures: Subjective pain scores (MacNab method Score).</td>
<td>6 months (excellent or good)</td>
</tr>
</tbody>
</table>

G1 = group 1; G2 = group 2; G3 = group 3; G4 = group 4; WK = week; RA = randomized; P = prospective; O = observational; DB = double blinded; B = blinded (patients or evaluator); U = unblended; R = retrospective; CT = tomography; VAS = Visual Analog Scale; MacNab method (excellent and good outcome); MRI/MR (magnetic resonance imaging).
ti-inflammatory drugs, as well as a significant improvement on the disability scale in the patient study group compared to the controls.

The outcome measures of the randomized studies were VAS (17,20), Backill scores (17) and drug intake (17), MacNab's criteria (15,20), and ODI (16,20).

2.2 Observational Studies

2.2.1 Methodological Quality Assessment

A total of 23 observational studies were considered for inclusion (Fig. 1). Only 8 of these met the methodological quality assessment criteria for inclusion (Table 5) (26-33). The results of the methodological quality assessment showed scores from 50 to 72. Some observational studies met the inclusion criteria, but had an insufficient score in the methodological quality assessment, and thus were only listed in the references (34-46). Furthermore, some studies were excluded for other reasons: one compared ozone therapy with a not well-established treatment (Alanerv) for low back pain (47); and Baabor et al (48) used another intervention associated with intradiscal ozone.

2.2.1 Descriptive results of observational studies

Among the observational studies, we observed heterogeneous groups of patients, different follow-up periods, and some discrepancy in the computed tomography (CT) or magnetic resonance imaging (MRI) evaluations of morphological criteria (Table 6). Muto et al published 3 studies between 1998 and 2008 (27,28,29) using intradiscal injection of an oxygen-ozone mixture under CT guidance to treat approximately 3,700 patients and reported an 80% success rate at short-term follow-up (6 months) and a 75% success rate at long-term follow-up (18 months), with no major or minor side effects.

Oder et al (26) studied 621 patients to determine associations among the morphology of the disc disease, patient-specific data, and treatment outcomes. Six hundred twenty-one consecutive patients were subjected to CT-guided ozonucleolysis in combination with periradicular infiltration by steroids under local anesthesia. Based on the MRI findings of the lumbar spine, the patients were retrospectively divided into 5 diagnostic groups: group I consisted of 205 patients (bulging disc); group II had 185 patients (herniated disc); group III had 66 patients (postoperative patients); group IV had 51 patients (primarily intervertebral osteochondrosis); and group V had 114 patients and included other primary nondiscal changes (intervertebral arthrosis, spinal canal stenosis and pseudoanterolisthesis). The patients received steroid and an oxygen-ozone mixture into the disc and periganglionic infiltrations by CT guidance. Each patient was monitored for a period of 6 months and documented with the Oswestry Disability Index (ODI) and VAS. Patients younger than 50 years had significantly better values on the VAS and in ODI scores, 6 months after treatment.

Andreula et al (30) reported a 78.3% success rate in patients treated with ozone therapy and periganglionic steroid injection compared with a 70.3% rate in those treated with ozone therapy alone; complications occurred in 2 of 235 patients and consisted of episodes of impaired sensitivity in the lower limb on the treated side, which resolved spontaneously within 2 hours. In a series of 45 patients, Buric et al (31) studied the differences in outcome between intradiscal ozone chemonucleolysis and microdiscectomy in patients with noncontained lumbar disc herniations; they documented that 27 patients (90%) in the chemonucleolysis group showed a statistically significant improvement in pain and function; the same was true in 14 (93.3%) patients in the microdiscectomy group. However, 2 patients dropped out of the ozone chemonucleolysis group because of aggravating symptoms and subsequently underwent surgery.

Das et al (33), in an Indian population cohort study, evaluated 53 consecutive patients with lumbar disc herniation. All presented with clinical signs of lumbar nerve root compression supported by CT and MRI findings. They were treated with a single session of intradiscal ozone therapy. Therapeutic outcome was assessed after 2 years. Pain intensity was significantly reduced following treatment (VAS baseline was 7.58; after 2 years, 2.64). Similar ODI results were seen (P < 0.05). No major complication was observed in this case series.

Xu et al (32) included 187 patients with sciatica and low back pain with positive Lasègue sign and diagnostic verification by CT and MRI exhibited disc protrusion with nerve root or thecal sac compression. They compared the effectiveness rates after one week (103 cases), 2 weeks (61 cases), and 4 weeks (23 cases) treatment sessions of intradiscal ozone therapy. They were evaluated by Macnab criteria at 48 months. The effective rate was 82.02% in all groups. However, there were no significant differences in the total effective rate in the 3 groups (P = 0.280).
Table 5. Methodological assessment of observational studies of ozone therapy

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Weighted Core Points</th>
<th>Author / country/year</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oder Austria 2008</td>
<td>Muto Italy 2008</td>
</tr>
<tr>
<td></td>
<td>Muto Italy 2004</td>
<td>Andruela Italy 2003</td>
</tr>
<tr>
<td></td>
<td>Muto Italy 1998</td>
<td>Buric Austria 2005</td>
</tr>
<tr>
<td></td>
<td>Xu China 2009</td>
<td>Das India 2009</td>
</tr>
</tbody>
</table>

| 1. Study Question | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| Clearly focused and appropriate question | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 | 2 |
| 2. Study Population | 8 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Description of study population | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Sample size justification | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| 3. Comparability of subjects | 22 | 11 | 11 | 14 | 14 | 14 | 14 | 11 | 14 | 14 |
| Specific inclusion/exclusion criteria for all groups | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Criteria applied equally to all groups | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Comparability of groups at baseline with regard to disease status and prognostic factors | 3 | 3 | 0 | 3 | 0 | 3 | 3 | 0 | 3 | 0 |
| Study groups comparable to non-participants with regard to confounding factors | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Use of concurrent controls | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Comparability of follow up among groups at each assessment | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Clear definition of exposure | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Measurement method standard valid and reliable | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Exposure measure equally in all study groups | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| 5. Outcome measures | 20 | 10 | 15 | 10 | 15 | 10 | 15 | 12 | 15 | 15 |
| Primary/secondary outcome clearly defined | 5 | 0 | 5 | 0 | 0 | 5 | 5 | 2 | 5 | 2 |
| Outcomes assessed blind to exposure or intervenient | 5 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 0 | 0 |
| Method of outcome assessment standard, valid and reliable | 5 | 5 | 5 | 5 | 5 | 0 | 5 | 5 | 5 | 5 |
| Length of follow-up adequate for question | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| 6. Statistical Analysis | 19 | 17 | 0 | 0 | 0 | 0 | 8 | 7 | 10 | 10 |
| Statistical tests appropriate | 5 | 5 | 0 | 0 | 0 | 0 | 5 | 5 | 5 | 5 |
| Multiple comparisons taken into consideration | 3 | 3 | 0 | 0 | 0 | 0 | 3 | 0 | 3 | 0 |
| Modeling and multivariate techniques appropriate | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 |
| Power calculation provided | 2 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Assessment of confounding | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Dose-response assessment appropriate | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 0 | 0 |
| 7. Results | 8 | 8 | 8 | 8 | 5 | 3 | 8 | 8 | 8 | 8 |
| Measure of effect for outcomes and appropriate measure of precision | 5 | 5 | 5 | 5 | 0 | 0 | 5 | 5 | 5 | 5 |
| Adequacy of follow-up for each study group | 3 | 3 | 3 | 3 | 5 | 3 | 3 | 3 | 3 | 3 |
| 8. Discussion | 5 | 5 | 0 | 0 | 0 | 5 | 5 | 3 | 5 | 5 |
| Conclusions supported by results with possible biases and limitations taken into consideration | 5 | 5 | 0 | 0 | 0 | 5 | 5 | 3 | 5 | 5 |
| 9. Funding or Sponsorship | 5 | 5 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Type and sources of support for study | _ | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

TOTAL SCORE 100 72 52 50 52 50 68 59 70

West et al. Rating system to measure the strength of evidence, evidence report, technology assessment No. 47 AHQR Publication No. 02-016 (11).
<table>
<thead>
<tr>
<th>Author/ Country/year/ Methods/Type of pain</th>
<th>Participants</th>
<th>Design of study/intervention (s) (guided by CT or fluoroscopy)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Das (33), India, 2009 Chronic</td>
<td>53 patients with low back pain due to lumbar disc prolapsed were included in this study</td>
<td>Prospective cohort study</td>
<td>Timing: 2 years Measure outcome: VAS and ODI</td>
<td>VAS (improvement of the 65.17%)</td>
</tr>
<tr>
<td>Xu (32), China, 2009 Chronic</td>
<td>187 patients with diagnostically confirmed lumbar disc herniation with sciatica and low back pain</td>
<td>Prospective study G1: (103) One week session G2: (61) 2 -week session G3: (23) 4-week sessions</td>
<td>Timing: 48 mos. Outcome measures: MacNab’s criteria Not reported</td>
<td>G1:82.52% G2: 85.24% G3: 95.65%</td>
</tr>
<tr>
<td>Muto (29), Italy, 2008 R, O Subacute</td>
<td>In 6 years, 2,900 patients with low back pain and/or sciatica refractory to medical management, lasting at least 2-3 mos. were treated with ozone and selected on the basis of clinical, psychological, neurological and neuroradiological criteria.</td>
<td>Patients divided into 4 groups: all procedures were carried out with: ozone (40µg/mL) intradiscal (3 – 4mL) and the foramen (10 mL). G1 (n=2,650) with soft - disc herniation; G2 (n=250) had calcified herniation; G3 (n=350) had multiple herniation and G4 (n=200) had FBSS</td>
<td>Timing: 6 and 12 mos. Outcome measure: VAS (-3 pts), MacNab’s criteria and ODI (-30%) Not reported</td>
<td>12 mos. (excellent and good) VAS:85% ODI: Significant reduction G1=75% G2 = Not reported G3=77% G4=60%</td>
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<tr>
<td>Oder (26), Austria, 2008 R, O Chronic</td>
<td>621 patients with lumbago or lumboschialgia and degenerative disease of the lumbar spine whose symptoms did not improve after previous conservative procedure</td>
<td>They were retrospectively divided into 5 diagnosis groups: G1 (n=205) Bulging disc; G2 (n=185) herniated disc; G3 n=66) post-operative patients; G4 (n=51) osteocondrosis and G5 (n114) non-disc disease (spinal canal stenosis, inter- vertebral arthrosis and pseudoanteriorlisthesis)</td>
<td>Timing:2 and 6 mos. Measure outcome: VAS and ODI Not reported</td>
<td>6 mos. (VAS) All patients improved: VAS: 31.8% ODI: Not measured</td>
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<tr>
<td>Buric (31), Italy, 2005 P, O Subacute</td>
<td>45 patients with acute or sub acute low back pain unresponsive to pharmacological treatment</td>
<td>The patients were divided into two groups G1(n=30) ozone inside the disc/30 mL – 30µg/ml G2 (n15) microdiscectomy</td>
<td>Timing: 6, 12 and 18 mos. Outcome measures: VAS, RMDQ, OPSR. MRI scans pre and post- treatment Not reported</td>
<td>18 mos. VAS (rate of improvement) G1=90%; G2=93.3% RMDQ: G1=90% G2=8606% OPRS:G1 79.3% G2=82.1% Morphological changes: 49% improved on MRI scan</td>
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<tr>
<td>Muto (28), Italy, 2004 R, O Subacute</td>
<td>2,200 patients with low back pain and/or sciatica refractory to medical management, lasting at least 2-3 mos., subjects were treated with ozone and selected on the basis of clinical, psychological, neurological and neuroradiological criteria.</td>
<td>Consecutive patients with degenerative disease, herniated disc, multiple disc herniation, FBSS, calcified disc herniation and disc associated with spinal stenosis received ozone (40µg/mL) intradiscal (3-4 mL) and the foramen (10 mL).</td>
<td>Timing6 and 18 mos. Outcome measures: Subjective MacNab’s criteria Not reported</td>
<td>6 mos. (excellent and good) G1=70.3% G2= 78.3%</td>
</tr>
</tbody>
</table>
Table 6 (cont.). Results of observational studies of ozone therapy for low-back pain

<table>
<thead>
<tr>
<th>Author/Country/year/Methods/Type of pain</th>
<th>Participants</th>
<th>Design of study/intervention (s) (guided by CT or fluoroscopy)</th>
<th>Outcome(s)</th>
<th>Result(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andreula (30), Italy, 1998 P, O, Subacute</td>
<td>600 patients with chronic low back pain resistant to conservative treatment, with positive signs of nerve root involvement, with or without hypoesthesia or paraesthesia, with appropriate dermatome distribution and CT or MRI findings in live with the patient's clinical picture</td>
<td>The patients were divided into two groups: G1(n=211) ozone Intradiscal/4ml and periganglionic/8ml-30µg/ml G2(n=235) ozone + steroid</td>
<td>Timing 6 mos.</td>
<td>Not reported</td>
</tr>
<tr>
<td>Muto (27), Italy, 1998 P/O Subacute</td>
<td>93 patients with low back and/or sciatica, lasting two or more mos., were treated with ozone</td>
<td>The patients were divided into two groups and all received ozone =15m;30µl/mL intradiscal and intraforaminal G1(n=35) with neurological deficit G2(n=58) without neurological deficit</td>
<td>Timing: 6 mos. Measure outcome MacNab's criteria</td>
<td>6 mos. (good or excellent) G1 = failure in all patients G2 = success in 77.58% of patients</td>
</tr>
</tbody>
</table>

G1 = group 1; G2 = group 2; G3 = group 3; G4 = group 4; RA = randomized; P = prospective; O = observational; DB = double blinded; B = blinded (patients or evaluator); R = retrospective; FBSS = failed back surgery syndrome; CT = tomography; VAS = Visual Analog Scale; ODI = Oswestry Disability Index; McGill = McGill questionnaire of pain; MacNab method (excellent and good outcome); RMDQ = Roland-Morris Disability Questionnaire; OPRS = Overall Patient Rating Scale; MRI/MR (magnetic resonance imaging); EMG (electroneuromyography).

The outcome parameters utilized in the observational studies were MacNab criteria (29,32), VAS (26,31,33), ODI (26,29), Roland-Morris (31), and Overall Patient Rating Scale (31). Three authors utilized CT/MRI in their follow-ups (27,28,31) (Table 6).

### 2.3 Effectiveness

Overall, the observational studies revealed positive results for short- and long-term relief of pain. From the randomized studies, intervention was found superior to the control, with OR 2.66 (95% CI, 1.94 to 3.63), and P < 0.00001 as shown in Fig. 2.

These studies evaluated ozone applied at the paravertebral muscle and juxtaforaminal at the herniated disc level. Three of them compared ozone injections utilizing an active control group (steroid injections) (14,15,16). Paoloni et al (17) utilized a sham control group with a simulated injection that was administered using a false needle that pricked the skin without piercing it, applied at the lumbar paraspinous level, on the same site designed to reproduce the load sensation commonly described after O2-O3 injections.

### 2.4 Level of Evidence

The indicated level of evidence is II-3 for ozone therapy applied intradiscally and II-1 for ozone therapy applied paravertebrally on long-term relief in low back pain secondary to disc herniation (12).

### 2.5 Recommendations

Based on Guyatt et al (13), grading the strength of recommendations and quality of evidence in clinical guidelines, the recommendation is 1C for ozone therapy applied intradiscally and 1B for ozone applied at the paravertebral muscles or periforaminally.

### 2.6 Complications

Complications secondary to ozone therapy are rarely documented in the literature. In this review, regarding ozone therapy for low back pain, we encountered predominantly case reports of 5 different types of complications. Giudice et al (22) reported bilateral vitreo-retinal hemorrhages following ozone therapy for lumbar disc herniation. Furthermore, one case of thunderclap headache after oxygen-ozone therapy
related to pneumoencephalus as a consequence of inadvertent intrathecal puncture was recently published (24). Ginanneschi et al (23) reported a case of a patient who experienced paresthesias along the anterolateral compartment of the left leg and hypoesthesia over the dorsum of the left foot, suggesting spinal nerve injury occurring a few minutes after percutaneous intradiscal infiltration of ozone for L4-L5 disc herniation. In 2004, Corea et al (21) published a report of vertebrobasilar stroke during ozone therapy. In 2 of 235 patients, Andreula et al (30) reported episodes of impaired sensitivity in the lower limb on the treated side, which resolved spontaneously within 2 hours. Fabris et al (34) reported a subcutaneous hematoma at the puncture site.

3.0 Discussion

The present review has added methodological improvements compared to previous review articles; the search database was wider and covered all languages, focusing on articles that used ozone alone in at least one group of patients. Final evidence was separated by the route of ozone administration. In addition, the authors performed a rigorous selection of RCTs that made possible a meta-analysis. Steppan et al (29) published a review in which data was extracted mainly from observational series; one was an unpublished study and one was a randomized trial on intradiscal ozone injections for the treatment of pain related to herniated discs. Although the authors have made a meticulous computation of data and wrote similar conclusions about the effectiveness and safety of this method, it probably would not be considered a meta-analysis if it had been submitted to the present review board.

Regarding the observational studies, 23 were initially selected according to the inclusion criteria, but only 8 could be included according to the rigorous methodological assessment criteria (11). Most studies lost points in the characterization of the study population because they did not specify the diagnosis. Probably, in future studies the authors should add diagnostic criteria and if needed, diagnostic procedures. The excluded studies also lack outcome measures and some of them had poor statistical analysis (which was absent in some of them). Furthermore, excluded studies contained heterogeneous populations of patients with low back pain, including patients with lumbar disc herniation, degenerative disease, acute pain, chronic pain, and patients with and without a history of operations. In addition, regarding the analysis of results, in some studies it was not clear what primary and secondary outcomes were expected; functional scales were diverse and in most cases not comparable. Most comparative studies used statistical analysis to aid the conclusions, but some of them have unacceptable confusion between normal and non-normal data distribution, resulting in the inappropriate choice of statistical tests. Furthermore, these studies often do not describe bias and limitations. Some studies include a large number of patients, a long period of follow-up and a careful surgical technique, but do not have appropriate design or statistical analysis (39). Another study did not compare with a method established in the literature, so it was excluded (46).

Among the selected RCTs, 3 of them compared ozone treatment with an active control group (steroid or steroid with local anesthetic) and one study compared ozone injection with a sham procedure. No placebo-control study was found among the articles included in this review. This seems to be a tendency when treatment-resistant pain is the issue. Currently,
ethics committees seem to favor studies based in an active controls comparison group. In addition, this makes patient recruitment faster because patients have a better acceptance when there is no placebo involved. Although this is not a consensus, it seems logical that an established treatment is probably better than the placebo effect. So, if any new treatment is to be tested, it could be perfectly compared to an active control group and in this way the placebo effect would also be overcome. On the other hand, patients tend to think that new treatments are more efficacious than the established ones because of their novelty. This makes us think that the novelty usually carries a strong placebo effect. This controversy still keeps placebo-controlled trials as the gold standard methodology. However, in the near future this methodological recommendation will probably be reviewed because practical issues point to more progressive methodology for active control studies in pain literature.

Some of the studies have evaluated the morphology of the disc by MRI or CT scan during follow-up. Buric et al (31) evaluated the clinical and morphological results of patients with disc disease and observed that 15 of the 30 patients showed clinical improvement, performing post operative MRI imaging. Eight of these patients had a substantial reduction of over 50% in herniation volume. Two patients had a volume reduction of less than 50%, whereas 5 patients had no substantial variation in herniation volume. Muto et al (27) observed a reduction in the size of the herniated disc in only 8 cases out of the 45 patients who had improved. In 2004, Muto et al (28) documented a reduction in herniated disc size in 63% of cases, confirming persistent satisfactory outcome. Thus, these authors stated that the equation large herniation = major symptoms, small herniation = minor symptoms, does not always hold true. It seems quite natural to assume that clinical signs and symptoms of disc herniation are not caused only by mechanical compression but that biochemical factors play an important role in inflammatory sensitization and immune response in the epidural environment of the nerve roots and ganglia. Based on the same reasoning, it seems logical to presume that mechanical removal of herniated tissue may not always be needed and that reducing the inflammatory process could essentially be sufficient to treat the symptoms. This hypothesis was partially confirmed by the cited study (49,50). On the other hand, patients who were clear candidates for surgery had no improvement after ozone therapy. Muto et al (27) observed treatment failure in all 35 patients previously selected for surgery who presented a herniated or protruded disc with radicular pain associated with neurological deficit. In the work of Buric (50), 2 patients dropped out of the ozone therapy group because of aggravating symptoms and were subsequently operated on. In another observational study (30), among patients treated with ozone and whose treatment had failed, outcomes were poor in 25% and poor with recourse to surgery in 4.7%. Among the patients in the steroid group and anesthetic injection group, 50 (16.7%) had poor results and 15 (5%) were referred for surgery.

The majority of the studies reviewed included patients with discogenic disease at one or more levels between L3 and S1(14-16,26,27,29-31). However, other series included heterogeneous groups of patients with other primary nondisc diseases such as canal stenosis, postsurgical fibrosis (failed back surgery syndrome), disc protrusion with vertebral instability, facet arthropathy, calcified herniation, intervertebral osteochondrosis, and pseudoanteriorlisthesis. In the first group, positive results were achieved in 75-80% of treated patients. In patients with a nondisc disease, the rate of sustained improvement ranged between 44 to 70% in all groups, independent of the morphological classification of the spinal disease (26,28,29). This suggests that ozone therapy may have an important role in low back pain relief, independent of the source of disease.

Ozone is a strong oxidizing agent that quickly reacts and oxidizes the proteoglycans in the nucleus pulposus, which results in a small reduction of disc volume and subsequently contributes pain relief. The suggested premise is that a small volume reduction results in a significant decrease in pressure. In addition, it has been shown to have anti-inflammatory/analgesic and natural antibacterial effects (5,52). Additional discussion of ozone’s mechanisms of action can be found elsewhere (51).

Ozone therapy for lumbar disc herniation is a procedure that is considered generally risk-free or as low as 0.1% (48) and has low or no adverse effects at concentrations used for therapeutic application (10-40 µg/mL). However, in the present review, 6 reports of side effects related to ozone infusion were found. Similar descriptions of transitory paresthesia suggested transient root dysfunction, although the mechanisms underlying the reported sensations are still not clear. Assuming the presence of microfractures of the annulus fibrosus, one possibility is that an abrupt, transient pressure spike in the region of the spinal canal and cerebrospinal fluid (CSF) pressure after disc infiltration could be related to
the transient paraesthetic symptoms. A similar mecha-
nism was postulated as the cause of acute bilateral
intraocular hemorrhages after injection of the O2-O3
mixture (22). Concerning the pathophysiology of the
lesion, it could be hypothesized that an abrupt and
transient increase of CSF pressure causes focal damage
by means of mechanical transmission of pressure in the
CSF, manifesting in the form of direct root trauma. The
occurrence of retinal hemorrhages immediately after
rapid injection of air into the subarachnoid space dur-
ing myelography or after epidural injection of cortico-
steroids has also been previously described (52,53).

Infection secondary to oxygen-ozone injection
therapy is extremely rare. Recently, Gazzieri et al (25)
reported a case of fatal septicemia secondary to Esch-
erichia coli infection after ozone therapy for lumbar
disc herniation, in which a pyogenic lumbar muscle in-
volveent and septic pulmonary embolism were pres-
ent. The most likely pathophysiological mechanism in
these cases was probably iatrogenic; that is, the direct
inoculation of the bacteria by injections due to an inad-
equate asepsis procedure as has occurred in other per-
cutaneous spinal procedures (25,30).

4.0 Conclusion

This systematic review and meta-analysis of ozone
therapy for low back pain secondary to herniated disc
indicated the level of evidence is II-3 for ozone thera-
py applied intradiscally and II-1 for ozone therapy ap-
plied at the paravertebral muscle and periforaminally
for long-term pain relief based on USPSTF criteria (12).
The available evidence yielded a 1C strength of recom-
mendation (13) for ozone therapy applied into the disc
and 1B for ozone applied at the paravertebral muscles
or periforaminally. The evidence was derived from ran-
domized control trials within this meta-analysis and ob-
servational studies. In addition, the low costs of ozone
therapy may account for its wider use in the percutane-
ous treatment of herniated lumbar discs (54) and other
causes of back pain. Injections can be repeated if neces-
sary and complications or side effects are rare. There-
fore, this method may be considered an option to treat
lumbar disc herniation-related low back pain that has
failed to respond to conservative treatment, represent-
ing an alternative to surgery. However, future studies
are necessary to demonstrate whether ozone therapy
effects persist over time.

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