Ozone Therapy as a Minimally-invasive Alternative in patients with Acute Lumbar Disc Herniation: A Randomized Clinical Trial

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Abstract

**Background:** Low back pain (LBP) management via conservative therapy with intervention fails in some cases. However, there are still many challenges to choose the best choice. Minimally-invasive techniques such as ozone therapy are emerging choices for surgery.

**Objective:** We evaluated the effects of ozone therapy on patients with LBP with protruding disc herniation who failed to respond to medical treatment.

**Methods:** In this Randomized phase III clinical trial (2017-19), one hundred patients admitted to Imam Reza Hospital (Tabriz-Iran) for herniated disk-induced LBP were randomly divided (shape- and color-identical envelopes) into two case and control groups. Patients in the case group were treated with ozone therapy (25 mcg/mL in 5 cc volume) plus medical therapy (naproxen 500 mg and baclofen 10 mg, both two times a day). Alternatively, patients in the control group received only conventional medical therapy. Primary outcomes such as changes in pain intensity (VAS) and basal test before and after treatment and also secondary outcomes like the amount of analgesic used were evaluated in the patients during two weeks, three months and six months after surgery. Student T-test and Chi-square were compared for comparing the data.

**Results:** Mean pain intensities estimated by VAS and improvement of restless leg syndrome were not significantly different between the two groups during two weeks \((p=0.8)\), three months \((p=0.5)\) and six months \((p=0.9)\) after the intervention. Pain intensity was found to be lower in both groups after the intervention compared with before treatment \((p=0.001\) for both). Moreover, significant differences were found between two groups in the Lasegue test during two weeks \((p=0.02)\) and six months \((p=0.01)\) after the intervention.

**Conclusion:** Application of ozone therapy not only improves clinical pain syndrome in LBP patients but also leads to improved medical treatment in these patients.

**Keywords:** Low back pain; Herniated disk; Ozone therapy; Medical therapy.

Introduction

Pain is one of the most unpleasant feelings that people may experience in their life. This pain can be appeared in different types, such as pain after surgery, cancer pain or pain in the spine and lower extremities.\(^1\)\(^2\) Acute lumbar disc herniation constitutes a range of common pathological disorders leading to Lumbar Back Pain (LBP). Herniation refers to extrusion of the nuclear part of the disk and rupture of the outer part due to various causes ranging from trauma to degeneration; whereby, degenerative joint and disc diseases are considered as the most common and important etiologies. The herniation is then complicated by nerve root compression, causing pain in patients.\(^3\)\(^5\)

Medical treatment with or without physiotherapy, as conservative approaches, are the first therapeutic stages to reduce pain in patients with disc herniation. Patients who did not respond to conservative therapy proceed to surgical or percutaneous minimally-invasive treatments.\(^5\) For half a century, surgical interventions such as discectomy were the standard procedures to manage disc herniation in patients with LBP. However, minimally-invasive techniques such as ozone therapy have recently been suggested as alternative procedures to reduce the need for open surgery. Over the past decades, the trend has been shifted towards these minimally-invasive techniques because of surgical complications, trauma and surgery-related costs.\(^6\)\(^8\)

Ozone \((O_3)\) gas is normally found in the earth atmosphere. Therapeutically, ozone is widely used as an antiseptic and antiviral agent. Upon injection into the disc material, ozone is rapidly disintegrated to \(O_2\) and \(O\). Accordingly, it reduces herniated disk volume and relieves pain. Although the exact mechanism of action is not clarified yet, it has been revealed that ozone possesses anti-inflammatory effects on disc herniation in patients with LBP. It also activated the
descending antinociceptive system, induce the release of endorphins, elevated the activation threshold of pain terminals, induce psychogenic stimulation of the central analgesic system, and involves in muscle relaxation and vasodilation by activating lactate metabolism and ATP production.5-7,9

Recent evidence suggested the therapeutic effects of ozone on disk herniation and the success rates were as high as 70-90% in different studies, and the side effects were estimated to be less than 0.1%. It has been also asserdominated that ozone therapy and medical treatment are equally effective in patients with severe acute LBP with partial motor weakness. In this regard, ozone therapy has been recommended in patients with LBP as an additional option for medical therapy who did not respond to medical management.10,11 However, these findings lack consensus among scientists.

Objectives

Here, we designed a randomized clinical trial to evaluate the effects of ozone therapy on patients with acute LBP and protruding disc herniation who suffered from radiculopathy and failed to respond to medical treatment.

Materials and Methods

Study Characteristics

A randomized phase III clinical trial was conducted at Imam Reza Hospital of the Tabriz University of Medical Sciences (TUOMS) to evaluate the impacts of ozone therapy on 100 patients referred due to LBP and protruding disc herniation who failed to respond to medical treatment between March 2017 and (Month) 2019.

Inclusion and Exclusion Criteria

Inclusion criteria were age between 18 and 60 years old, acute LBP with radiculopathy, Visual Analogue Scale (VAS) moderate to severe5-10 at least in one leg, and protruding disc herniation without disc degeneration confirmed by Magnetic Resonance Imaging (MRI). Acute LBP was defined as back pain in the last ten days and lack of symptom during three months before enrollment to the study. Also, radiculopathy was defined as referral pain to lower extremities started in the last ten days with no symptom during three months and positive Lasegue Test or Straight Leg Raise (SLR). Restless Leg Syndrome (RLS) was defined as a neurological disorder of sensorimotor origin resulting in “irresistible urge to move the body to relieve the uncomfortable sensations”.13

Claudication was defined as cramp and pain of a given muscle group happening only through exercise and exacerbating gradually as a given individual endures to walk until it urges him to completely stop moving.14 Exclusion criteria were extrude disc herniation, neurologic deficit, cauda equine syndrome, vertebral or canal stenosis, vertebral dislocation, malignancy, past history of spinal surgery, diabetes mellitus or other chronic disease, mental disorders, Body Mass Index (BMI) more than 30, spondylolisthesis, pregnancy or lactation, lumbar scoliosis more than 20 degrees, a difference between two lower limbs of more than 1.5 cm confirmed by X-ray imaging, Glucose-6-phosphate dehydrogenase deficiency, and recent ozone therapy.

Randomization method

All numbers from one to one-hundred were written shape- and color-identical envelopes. The envelopes were then packed and then given to the head nurse of department and distributed among patients. The given numbers matched with case and control groups numbers previously taken from statistics consultant.

Study Methods

In this prospective study, 100 patients were randomly divided into two case and control groups. Patients in the case group were moderately sedated in the operation room half an hour before the procedure by the anesthesiologist (member of research group) and then positioned prone. To render a convex shape to the lumbar discs, the table of operation was upwardly adjusted. Accordingly, antiseptic prepping and sterile draping were performed, and 27 cm spinal Chiba needle (18G) was introduced by the extra-articular and postero-lateral approach. In order to confirm the position of Chiba needle lateral and anteroposterior imaging were performed. The side of approaches was matched with MRI findings and patients radicular pain side.

Afterward, the ozone-oxygen mixture in 25 µg/5 mL dose was injected into the disk space between the prosthetic disk break and the nucleotide proteoglycan, so that the water was removed from the disk, and then the disk was collected. All procedures were performed under fluoroscopy guidance in each marked level, and the material was administered inside the nucleus pulposus. It should be noted that the intervention was performed by an anesthesiologist (member of the research group) to properly state the results of the study. The patients were hospitalized after surgery and discharged the next day. The patients were instructed to avoid returning to
work before seven days.

Ozone group also control received naproxen tablets (500 mg) per os two times a day and baclofen tablet 10 mg per os two times a day for six months. Control group received only the mentioned medications using the same dosage and route; however, no ozone therapy was implemented. Primary outcomes, e.g., changes in pain intensity (VAS) and basal test before and after treatment and also secondary outcomes, e.g., the amount of analgesic used were evaluated in patients after two weeks, three months and six months after the surgery.

Ethical Considerations

Written informed consent was obtained from all of the enrolled patients. Also, the contents of the present study were approved by the ethics committee of TUOMS (IR.TBZMED.REC.1396.286) and registered at the Iranian Registry of Clinical Trial center under reference number “IRCT20170727035336N1” code. This research was financially supported by the Tabriz University of Medical Sciences and the patients did not pay any costs.

Statistical analyzes

SPSS TM Software (version 25) was used for all statistical analyses. Descriptive statistics were shown by the mean, standard deviation (SD), frequency, and frequency percentage. Mean of values was compared using student T-test. Quantitative variables were compared using a repeated measure of ANOVA (repeated measures of variance analysis) between groups. Moreover, Chi-square and Fisher’s exact tests were used for comparing the qualitative data. P value less than 0.05 was considered statistically significant.

Results

Demographic findings

In a randomized clinical trial, one hundred patients with lumbar discopathy were enrolled and randomly divided into two case (medical treatment and ozone therapy) and control groups (medical treatment). Fifty-three patients were male, and 47 patients were female. A significant difference was found in six between the treated and control groups (p=0.02). However, no significant difference was shown between two groups in age, weight, height and also BMI (p=0.07, p=0.36, and p=0.07, (p=0.09), respectively). (Table-1).

Primary outcomes

Pain intensity estimated via VAS grading and mean pain intensity was higher in the control group at admission; however, the difference between the two groups did not reach statistical significance upon admission (p=0.2). Further analysis showed that the mean pain intensities estimated by VAS were not significantly different between the two groups at two weeks, three months and six months after intervention (Table-2 and Figure-1).

It was also found that the Lasegue test or SLR at enrollment was higher in the treated group, but there was no statistically significant difference between the two groups (p=0.15). However, significant differences were found between two groups in the Lasegue test at two weeks and six months after intervention (Table-3 and Figure-2).

Table-4 shows the progress of pain reduction and lasegue test improvement in the treated and control groups. The results revealed that pain intensity and lasegue test were significantly lower and higher, respectively in two weeks after treatment vs. admission, three months after treatment vs. two weeks after treatment, and six months after treatment vs. three months after treatment (for p values, please refer to the tables).

All 100 patients in the both treated and control groups had RLS at enrollment. We showed no significant differences in the improvement of RLS between the two groups after two weeks, three months, and six months.

However, a significant difference was found between the two groups in claudication at enrollment and two weeks after intervention. There were no patients with claudication during six months follow-up period (Table-5).

| Table-1. Demographic information of patients investigated in the present study |
|---|---|---|---|
| Variables | Treated group | Control group | P value |
| Sex | Male | 32 (64%) | 21 (42%) | 0.02 |
| | Female | 18 (36%) | 29 (58%) | |
| Age (years) | 48.28 ±6.82 | 50.64 ± 6.17 | 0.07 |
| Body Weight (Kg) | 78.16 ± 4.26 | 79.08 ± 4.85 | 0.36 |
| Height (Cm) | 169.42 ± 6.95 | 167 ± 6.35 | 0.07 |
| BMI (Kg/cm²) | 27.31 ± 2.33 | 27.45 ± 2.54 | 0.09 |
Table-2. Mean pain intensity estimated by VAS grading at enrollment, two weeks, three and six months after the intervention. Visual Analogue Scale (VAS).

<table>
<thead>
<tr>
<th>Mean VAS</th>
<th>Treated group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upon admission (Range)</td>
<td>7.26±0.69 (5-8)</td>
<td>7.68±0.47 (7-8)</td>
<td>0.2</td>
</tr>
<tr>
<td>2 weeks Later (Range)</td>
<td>6.94±0.93 (5-8)</td>
<td>7.18 ± 0.85 (5-8)</td>
<td>0.8</td>
</tr>
<tr>
<td>3 months later (Range)</td>
<td>5.54±1.34 (5-8)</td>
<td>5.94±1.5 (5-8)</td>
<td>0.5</td>
</tr>
<tr>
<td>6 months later (Range)</td>
<td>5.3±1.79 (4-8)</td>
<td>5.24±1.66 (5-9)</td>
<td>0.9</td>
</tr>
</tbody>
</table>

Table-3. Lasegue test at enrolment, two weeks later, three months later and six months later. Numbers represent the degree of the extension during test.

<table>
<thead>
<tr>
<th>Mean Lasegue test</th>
<th>Treated group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upon admission (Range)</td>
<td>42.3±8.4 (30-60)</td>
<td>41.4±11.95 (30-60)</td>
<td>0.15</td>
</tr>
<tr>
<td>2 weeks Later (Range)</td>
<td>47.4±10.65 (30-60)</td>
<td>51.9±9.68 (30-60)</td>
<td>0.02</td>
</tr>
<tr>
<td>3 months later (Range)</td>
<td>53.4±8.11 (30-60)</td>
<td>51±10.5 (30-60)</td>
<td>0.6</td>
</tr>
<tr>
<td>6 months later (Range)</td>
<td>57±6.78 (30-60)</td>
<td>51.3±10.96 (30-60)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Table-4. Comparison of pain reduction and lasegue test improvement progress in case and control group in three follow-up periods. VAS, Visual Analogue Scale (VAS).

<table>
<thead>
<tr>
<th>Variables</th>
<th>Treated group</th>
<th>Control group</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>enrollment vs. 2 weeks</td>
<td>p=0.001</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>2 weeks vs 3 months</td>
<td>p=0.0001</td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td>3 months vs 6 months</td>
<td>p=0.0001</td>
<td>p=0.0001</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variables</th>
<th>At enrollment</th>
<th>Two weeks</th>
<th>Three months</th>
<th>Six months</th>
</tr>
</thead>
<tbody>
<tr>
<td>RLS</td>
<td>Treated (%)</td>
<td>50(100%)</td>
<td>48(96%)</td>
<td>17(37%)</td>
</tr>
<tr>
<td>Control (%)</td>
<td>50(100%)</td>
<td>50(100%)</td>
<td>24(48%)</td>
<td>8(16%)</td>
</tr>
<tr>
<td>P value</td>
<td>-</td>
<td>0.15</td>
<td>0.11</td>
<td>0.63</td>
</tr>
<tr>
<td>Claudication</td>
<td>Treated (%)</td>
<td>27(54%)</td>
<td>17(34%)</td>
<td>2(4%)</td>
</tr>
<tr>
<td>Control (%)</td>
<td>10(20%)</td>
<td>5(10%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>P value</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>-</td>
</tr>
</tbody>
</table>

Figure-1. Pain tests result in different times
Discussion

This study was performed with the aim of ozone therapy as a minimally-invasive alternative in patients with acute lumbar disc herniation. A clinical syndrome known as acute LBP that follows herniated lumbar disk has a tendency to vanish in almost half of the patients. However, it is not possible for all patients to endure such drastic a pain for quite some time before it improves. The short and long-term success rates for surgery are around 95-98% and 80%, respectively. This picture is further complicated by Failed Back Surgery Syndrome (FBSS), which causes severe symptoms in 20% of the subjects. Newer minimally invasive techniques such as chemonucleolysis with chemopapain, discectomy LASER, nucleoplasty, and last but not least ozone therapy have been developed to respond for such as demand.\(^{15}\) Upon disk herniation, due to the exposure of segregated proteoglycan component of nucleus pulposus, an inflammatory response is initiated which increases the adjacent nerve sensitivity to the pain. It has been shown that ozone administration increases oxygen levels in the injured site, decreases nucleus pulposus volume by water drainage, and enhances microcirculation, all of them can improve the symptoms experienced by the patients.\(^{16}\) However, these findings are not universal. Accordingly, we designed a randomized clinical trial to evaluate the added benefits of ozone therapy on patients with LBP and protruding disc herniation who failed to respond to medical treatment with Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and muscle relaxants. Our results showed no significant difference in pain intensity and RLS between ozone plus medical treatment and medical treatment only groups at different follow-up periods. Lasegue test performance and claudication were improved in the ozone group though. The results also revealed that pain score and Lasegue test performance were significantly improved after treatments compared with the conditions before these interventions in the both groups. These results advocate the fact that ozone therapy at least partially adds some benefits to conventional medical therapy in patients with acute LBP due to protruding disk. This may subsequently reduce the need for sequential surgeries saving costs and avoiding operation-associated complications. A randomized clinical trial performed on 159 patients with sciatica compared with the therapeutic effects of intraforaminal and intradiscal injections consisting of a steroid, a local anesthetic, and oxygenoxide (27 mcg/mL in 12 cc volume vs 25 mcg/mL in 5 cc volume in our study) mixture with intraforaminal and intradiscal administration of a steroid and an anesthetic without ozone. This study showed that treatment was successful in 74% of the patients in the former and 47% of the patients in the latter, where the difference reached statistical significance at six months. The authors concluded the superiority of ozone-containing mixture to the other treatment.\(^{17}\) Xu et al., performed almost the same study and replicated the same results.\(^{18}\) Consistent with these findings, our study showed that ozone therapy plus an NSAID and muscle relaxant is at least partially superior to those medications that are used alone in the treatment of acute LBP.

Paoloni et al., assessed the effects of intramuscular injection of oxygen-ozone in the treatment of acute LBP due to disc
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Sixty patients were enrolled in this study, and the results were compared with the control group. This study showed that the number of pain-free patients was remarkably lower in the ozone group than that of the control group. Also, patients who received ozone therapy had lower mean pain score (VAS) than the patients who received simulated therapy over the study course. These results were consistent with our findings, which proved the effectiveness of ozone therapy in LBP patients. However, in our study, the pain score (VAS) was not different between the two groups at various follow-up intervals. The difference may be attributed to the fact that our study assessed the added effects of ozone therapy on NSAID therapy in patients who do not respond to the latter.

Zhang et al., compared the therapeutic impacts of intradiscal and intraforaminal injection of oxygen-ozone alone with oxygen-ozone/betamethasone mixture in 172 consecutive adult patients suffering from herniated disk-induced LBP. This study showed that pain experienced by the patients quantified by VAS and Japanese Orthopedic Association’s evaluation system for lower back pain syndrome (JOA score) was significantly lower after treatments compared with the conditions before intervention. Also, no meaningful difference was found between two groups at three weeks, six and 12 months follow-up period. These results were in agreement with our finding, which proved the therapeutic efficacy of ozone therapy in these patients.

In another study, Muto et al., evaluated the therapeutic effects of intradiscal and intraforaminal oxygen-ozone (O2-O3) injection in 2200 patients with LBP due to disk herniation. This study showed that ozone therapy is an effective treatment in these patients. The results of this study indicated an 80% success rate and a 20% failure rate in 1750 patients in six months 75% success rate and a 25% failure rate in 18 months. However, this study suffered from a lack of a control group and did not assess the effects of ozone therapy in patients who do not respond to conventional medical therapy. The failure was most commonly attributed to spinal canal stenosis, recurrent disk herniation accompanied by fibrosis, and calcification of herniated disk.

A systematic review and meta-analysis of 12 randomized controlled trials showed that long-term pain relief potency of ozone therapy is supported by evidence level of II-3 (1C recommendation level) for intradiscal and evidence level of II-1 (1B recommendation level) for paravertebral ozone therapy for LBP secondary to a herniated disc. However, this study did not assess the added benefits of ozone therapy in patients with response failure to medical therapy. In a systematic review and meta-analysis of randomized clinical trials by de Andrade et al., it was demonstrated that ozone therapy was more effective on the reduction of the symptoms of LBP compared with radiofrequency and also triamcinolone injection both in acute phase and six months after treatment. However, the difference between various therapies was not significant at 3-month period. This study found that ozone therapy is a safe procedure compared to the other methods. Nevertheless, this procedure has some complications that range from subcutaneous hematoma at the puncture site to vertebrobasilar systemic stroke. The results of the mentioned study were consistent with the findings of the present study.

Conclusions
In general, the findings of the present study confirmed the effectiveness of ozone therapy in the treatment of LBP and lower extremity symptoms relief due to a herniated disk in patients who do not respond adequately to medical therapy. However, none of the mentioned studies had assessed the superiority of ozone therapy combination with NSAIDs/relaxant to the latter treatment alone. Our study showed that the addition of ozone therapy at least partially adds benefit to the medical treatment in these patients.

This study has several limitations, which should be addressed well in future studies. These limitations included a limited number of cases, lack of experimental procedure blinding, and lack of placebo control.

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Authors’ Contribution
All authors pass the four criteria for authorship contribution based on the International Committee of Medical Journal Editors (ICMJE) recommendations.
Conflict of Interests
The authors declared no potential conflict of interests with respect to the research, authorship, and/or publication of this article.

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