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Research Article

# Efficacy of Lumbar Transforaminal Epidural Steroid Injection with or without Ozone Therapy on Radicular Pain

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**ABSTRACT**

**Background:** The effect of ozone therapy in reducing inflammation and radicular pain with lumbar transforaminal epidural steroid has not been sufficiently investigated. This study compares the effectiveness of transforaminal steroid injection with or without ozone therapy on radicular (leg) pain.

**Methods:** In a double-blind clinical trial, 40 patients with chronic radicular pain whose pain did not respond to conservative treatments were selected and randomly assigned to two treatment groups of A and B. Group A underwent transforaminal epidural steroid injection with ozone and group B underwent transforaminal epidural steroid injection without ozone. The intensity of pain with the Numerical Rating scale (NRS) scale and the degree of disability with the Oswestry Disability Index (ODI) questionnaire were compared in both groups of patients before treatment, 24 hours after treatment, 1 and 3 months after treatment.

**Results:** Both groups of A and B were similar in terms of age, gender, pain duration, pain intensity and disability before treatment (P>0.05). In treatment groups of A and B the mean of pain score 24 hours after treatment was 6.95±2.50 and 6.15±3.50 (P=0.495), one month after treatment it was 4.10±2.59 and 3.25±2.32 (P=0.355) and the third month of treatment was 3.85±3.01 and 3.55±3.25 (P=0.429). respectively. The mean of ODI 24 hours after treatment was 22.50±10.78 and 18.95±15.24 (P=0.401), one month after treatment it was 19.40±7.76 and 7.95±5.42 (P <0.001) and three months after treatment it was 17.40±7.26 and 13.55±8.70 (P=0.137).

**Conclusion:** It seems that adding ozone to corticosteroids has very little effect in reducing pain, and it did not have a significant effect at least in the study. One of the reasons may be the limitation of the sample size in the study, so it is suggested to conduct more studies in this field.

## Introduction

Lumbar radicular pain is a type of neuropatic pain which is caused by stimulation of the sensory root or dorsal root ganglion of the nerve. Lumbar radicular pains are caused by the generation of aberrant impulses in the dorsal root ganglion and transmission through the axon of peripheral nerve [1]. The role of neuroinflammation in chronic lumbar radiculopathy remains unknown. Clinically, the assumption of an inflammatory component in the pathophysiology of chronic sciatica, and specifically at the nerve roots' surface, is the rationale for using epidural anti-inflammatory steroid injection (ESI) as a therapeutic strategy for the disorder. However, the treatment shows different successes [2].

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The treatment of radicular symptoms varies from lifestyle change and protective treatments to surgical interventions. Epidural steroid injection, radiofrequency pulse and surgery can be mentioned among the treatment methods for radicular back pain [3-4]. Epidural steroid injection is one of the most common non-surgical interventions prescribed for the symptoms of back pain with leg pain [5]. Although ESI is widely used, its effectiveness in patients with radicular pain is different [6]. Based on the available scientific evidence, epidural steroid injection in a short period leads to improvement of radicular pain. Studies have also shown that epidural steroid injection is effective in improving the symptoms of secondary radicular pain to spinal canal stenosis. Of course, epidural injection is the most common control intervention for chronic back pain and limb pain, secondary to disc herniation and other pathologies [3].

Epidural injection is performed with different interlaminar, caudal and transforaminal methods. These three methods have considerable differences [7-8]. In the interlaminar method, the drug is injected near the area that is assumed to be pathological, while in the transforaminal method, the intervention is performed specifically at the target location, and a smaller volume of drug is injected to reach the initial pathological location. Among the advantages of the transforaminal method, we can point to the specific location of pain and use of the smallest volume of injection drug to reach the primary site of pathology, which is the anterior-lateral epidural space. Epidural injection by the transforaminal method in comparison with the caudal and interlaminar method is associated with a significant risk, which includes damage to the segmental artery and the dorsal root ganglion and the related spinal nerve. Transforaminal epidural injection can be used for various cases such as lumbar radiculitis with or without herniated disc, discogenic pain, spinal stenosis and post-surgical failure syndrome (FBSS) [9-10].

Ozone is actually a combination of ozone and oxygen (O3/O2) and ozone makes up less than 5% of the mixture. One of the properties of ozone is its germicidal effect and it can disinfect water. Ozone therapy has been known since the 19th century and is used topically, intramuscularly, intravenously, rectally, and subcutaneously. Topical and subcutaneous, intramuscular and intra-articular use of ozone has regional and intravenous effects, and its rectal use has systemic effects [11].

Ozone by intradiscal, subcutaneous, paravertebral injection with dehydration and disc pressure reduction is effective in reducing pain. Ozone is oxidative and ten times more soluble than oxygen. That's why, it has the ability to penetrate and spread immediately in the tissues. Immediately after facing to the tissue, it reacts and by creating a buffering antioxidant, it also has an anti-inflammatory and pain-relieving effect. Ozone makes erythrocytes flexible and facilitates the release of oxygen to tissues. Ozone increases tissue ATP and causes an increase 2 and 3 diphosphoglycerates and shifts the oxyhemoglobin diffusion curve to the left. It also reduces blood viscosity and has anti-adhesion properties in platelets [12].

The amount of pain reduction caused by ozone is evaluated between 50-60%. It has been used to relieve pain in shoulder and knee areas, transforaminal epidural and intradisc. Ozone in the form of a mixture (O3/O2) with a non-toxic dose of 1 to 40 micrograms is used to reduce inflammation around the nerve root [13].

Recently, it has been stated that ozone therapy also produces analgesic effects by the mechanism of reducing inflammation and increasing oxygen delivery to the damaged tissue [14]. ozone therapy reduces the serum level of anandamide which in this case the production of anandamide, which is the main ligand of cannabinoid receptors, increases. On the other hand, due to the activation of the endocannabinoid pathway [15], it has been reported that ozone therapy, despite having anti-inflammatory and analgesic properties, can increase an individual's ability to perform physical activity [16].

Currently, studies have shown that epidural steroids are effective in the inflammatory origin of pain, as its short-term effect has been proven, while ozone is effective in the short-term and long-term, ozone reliefs pain in the short-term due to its anti-inflammatory effect and in the long term due to its property in denaturing the proteins of the disc material and correcting the underlying pathology that led to the pain, it causes long-term pain relief. Studies have also shown cumulative effects of ozone and epidural steroids [17]. However, the positive effects of ozone therapy, especially in reducing inflammation and pain, are still unknown to many doctors, so in the present study, the effect of transforaminal epidural steroid injection with and without ozone was investigated and is compared in patients with radicular (leg) pain.

## Methods

In this clinical trial the study, patients were investigated who referred to Shariati and Amir Alam Hospital in Tehran due to chronic radicular pain for more than 3 months and their pain did not respond to conservative treatments, if the patient met the inclusion criteria; after obtaining written and informed consent, their demographic characteristics were recorded in the questionnaire and their pain score was evaluated with the Numerical Rating scale (NRS) scale and the disability level questionnaire with the oswestry disability index (ODI). Then they were randomly assigned to group A or B using the envelope method. Patient selection and follow-up are shown in (Figure 1).

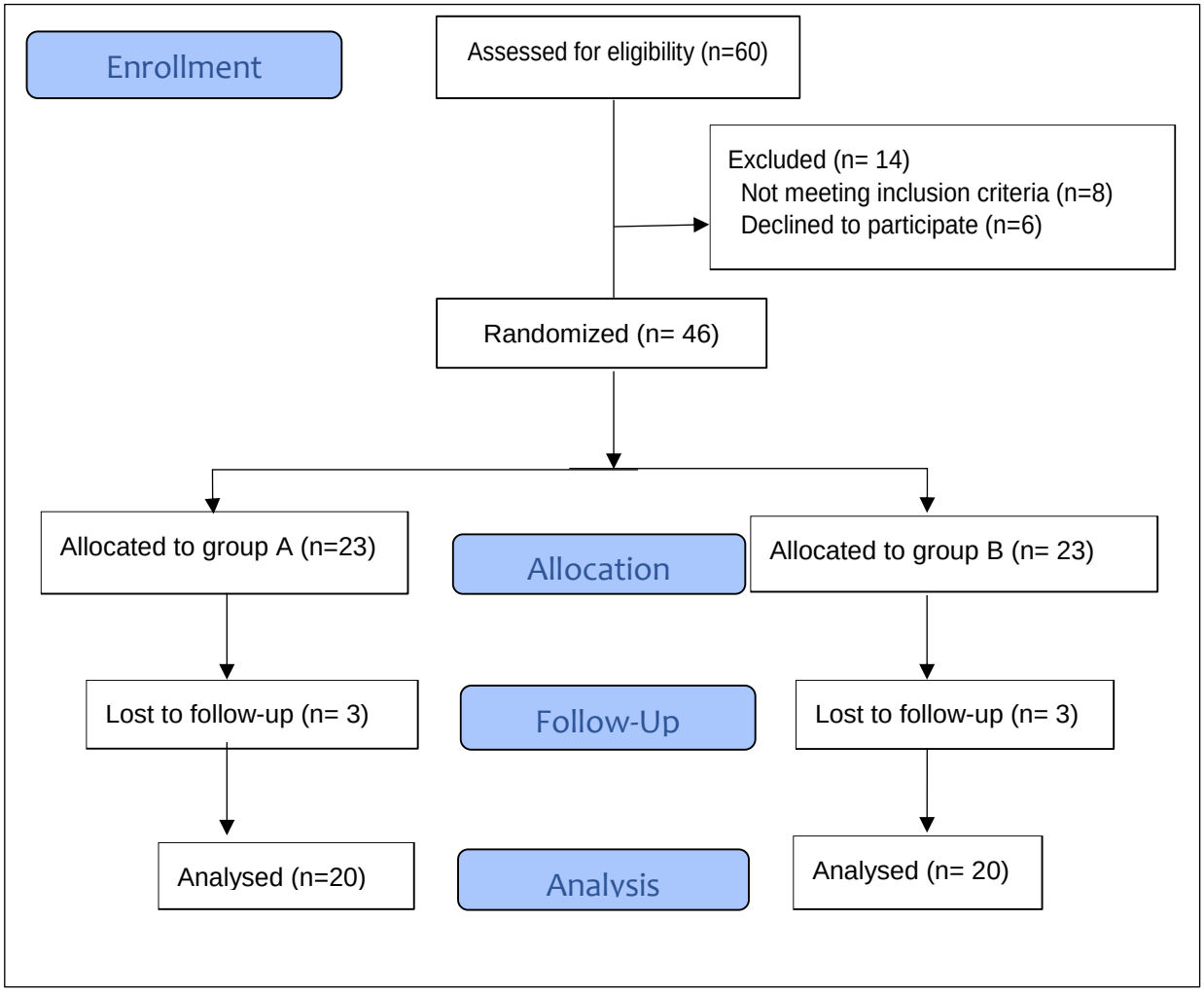


**Figure 1- Diagram of the study design**

Group A underwent transforaminal epidural steroid injection with ozone and group B underwent transforaminal epidural steroid injection without ozone. All epidural steroid injections were performed in the operating room by the attending physician under aseptic conditions. For this purpose, the patient was placed in the prone position, a pillow was placed under the pelvis and a support was placed under the ankles. The halluxs should be close together and the heels should be far apart. Standard monitoring including blood pressure, ECG and pulse oximetry was performed during the injection. An intravenous line was established and intravenous sedation with fentanyl were prescribed. The initial dose of midazolam was up to one milligram intravenous and 50 micrograms of fentanyl based on the patient's condition and during the procedure, it was repeated as needed, in such a way that verbal communication with the patient was also possible. After scrubbing, the doctor disinfects the area (waist, sacrum, and buttocks) with betadine, wearing a sterile gown, gloves, hat, and mask, and covers the patient's body with a sterile gown from the upper thoracic region to the knees. the target was identified under fluoroscopic guidance and inserted with needle, and then contrast material with a concentration of 240 mg/ml was injected to ensure the correct location of the needle.

Lumbar transforaminal epidural steroid injection with and without ozone on the side of the patient's symptoms (pain) and on the surface of the involved nerve root (L4/L5/S1 dermatome) was performed after contrast agent injection and fluoroscopy confirmation in the epidural space as follows [21]. The total volume is 4 ml (2 ml of triamcinolone 40 mg/ml and 2 ml of bupivacaine 0.125%) in groups A and B, plus 3 ml of ozone with a density of 20 μg/ml only in group. Both groups of patients were re-evaluated 24 hours after injection, 1 and 3 months after injection in terms of pain and disability.

**Inclusion criteria& exclusion criteria**

The presence of radicular pain for at least 3 months, a pain score of more than 4 on the NRS scale, non-responsiveness to non-invasive treatments and the patient's consent to participate in the study. Rheumatic diseases, acute trauma and spinal fracture, malignancies,

mental diseases, peripheral neuropathy, urinary and fecal incontinence, hyperthyroidism, infection, and favism were considered excluded criteria.

**Randomization and blinding method**

In order to randomize, 40 cards were used, on 20 of which had been written letter A means transforaminal epidural steroid with ozone and on the other 20 of which had been written letter B means transforaminal epidural steroid without ozone. The cards were placed in an envelope with aluminum foil. Upon the visit of a qualified patient, one of the envelopes is randomly selected and opened, according to the chosen letter (A or B inside), the patient is assigned to the transforaminal epidural steroid group with ozone or without ozone. In the study, the outcome assessor and the patient were unaware of the assigned treatment group (double-blind study).

Sample size

Based on Krahulik et al [18] for calculating sample size, $\alpha = 0.05$ and $\beta = 0.2$ with power 80. %, the sample size was determined to be 20 people in each group and 40 people [18].

**Ethical considerations**

In all patients, written consent was obtained before starting the study. The Tehran University of Medical Ethics Committee approved this study Sciences (IR.TUMS.NI.REC.1401.052); also, this study is registered in the Iranian Registry of Clinical Trials (IRCT20151123025202N28).

**Statistical Analysis**

In order to analyze the data, SPSS version 26 software was used. Descriptive information related to qualitative variables were displayed in the form of tables and graphs, and descriptive information of quantitative variables were displayed in the form of central and dispersion indices. In order to compare qualitative variables in two groups using Chi-square test and Fisher's exact test and the amount of intensity changes in two groups before the intervention, 24 hours and 1 and 3 months after the intervention, independent t-tests and analysis of variance of observations with repeated measurement was used. All analyzes were performed at a confidence level of 95% and P.value <0.05 was considered significant.

## Results

In patients with radicular pain undergoing transforaminal epidural injection with and without ozone, the mean and standard deviation of age were 50.75±9.67 and 52.45±15.26 years (P=0.677) respectively. In group A, 11 people (55%) and group B, 9 people (45%) were men (P=.0527). The two groups were similar in terms of history of drug use (P=0.098), Tf level (P=0.701), side of involvement (P=0.430) and MRI findings (P=0.098).

The frequency of analgesic use in patients undergoing epidural transforaminal steroid injection with and without ozone was 45 and 55% before the intervention (P=0.527) and 35 and 35% after the intervention (P=1.00).

Between patients with radicular pain undergoing transforaminal epidural steroid injection with and without ozone in terms of symptom duration, axial pain intensity before treatment, 24 hours, 1 month and 3 months after treatment and radicular pain intensity, before treatment, 24 hours, 1 month and 3 months after treatment, no significant difference was observed (Table 1).

Based on the results of the t-test between the group under transforaminal epidural steroid injection with and without ozone no significant difference was observed in terms of the mean intensity of axial pain on the first day (P=0.758), the end of the first month (P=0.328) and the end of the third month of treatment (P=0.583). Based on the result of the covariance test with repeated measurements, and using the axial pain size before treatment (baseline) as a covariate, a significant difference was observed between the group with and without ozone over time in terms of changes in axial pain (P=0.036). Also, in each group, the pain score decreased significantly (P=0.018) compared to before treatment (Figure 2).

Based on the results of the t-test, no significant difference was observed between the group under epidural transforaminal steroid injection in terms of mean of radicular pain in 24 hours, at the end of the first month and at the end of the third month of treatment. Also, based on the result of covariance test with repeated measurement, and setting the radicular pain size before treatment (baseline) as a covariate, no significant difference was observed between the intervention and control groups over time in terms of radicular pain changes. However, in both groups, the intensity of radicular pain was significantly reduced compared to before treatment (P=0.040) (Figure 3).

Based on the results of the t-test, no significant difference was observed between the group under transforaminal epidural steroid injection in terms of the severity of disability caused by radicular pain 24 hours and at the end of the third month of treatment. But at the end of the first month, the intensity of disability in the group without ozone therapy was significantly lower than the group under ozone therapy (P<0.001) (Figure 4). Based on the result of the covariance test with repeated measurements, and using the disability size before treatment (baseline) as a covariate, no significant difference was observed between the two groups over time in terms of changes in the severity of disability. Also, in both groups, the severity of disability caused by radicular pain was not significantly different compared to before treatment (Table 2).

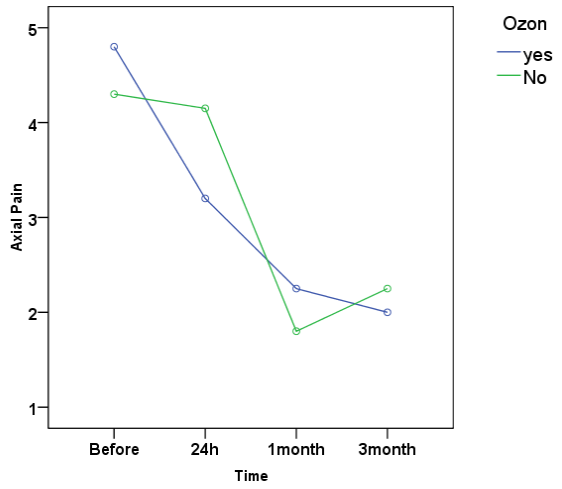


**Figure 2- Changes in the score average of pain intensity of axial in patients with radicular pain under tranceforaminal epidural steroid injection with and without ozone therapy before and after treatment.**

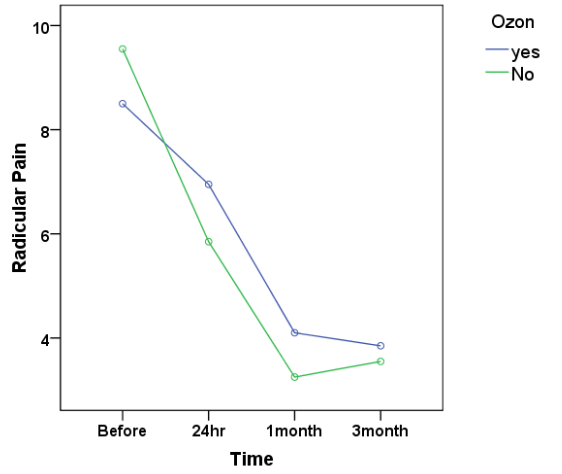


**Figure 3- Changes in average of pain intensity of radicular in patients under transforaminal epidural steroid injection with and without ozone therapy before and after treatment**

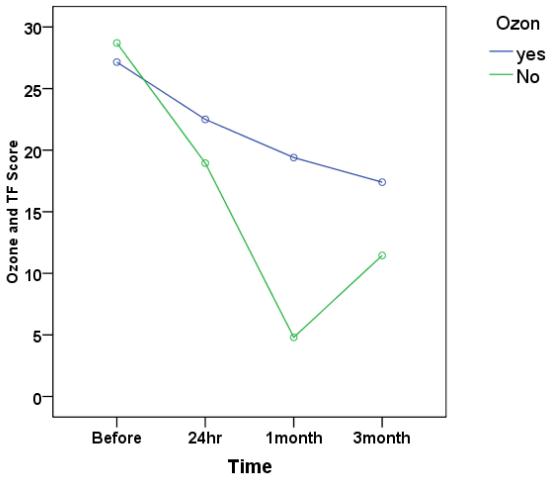


**Figure 4- changes in average of disability intensity in patients under transforaminal epidural steroid injection with and without ozone therapy before and after treatment**

**Table 1- Frequency of duration of symptoms, axial and radicular pain before and after treatment of patients with radicular pain under transforaminal epidural steroid injection with and without ozone therapy**

| Variable | Group A | Group B | P (Mann-Whitney) |
|---|---|---|---|
| Duration of pain | 44.3±40.8 | 34.4 ±6.8 | 0.174 |
| Axial Pain NRS Basic | 4.8 ±4.6 | 4.3±4.2 | 0.758 |
| Axial Pain NRS 24h | 4.2±3.2 | 4.1±3.7 | 0.327 |
| Axial Pain NRS 1month | 2.2±2.9 | 1.8±1.8 | 0.583 |
| Axial Pain NRS 3month | 2.0±2.5 | 2.2±2.5 | 0.445 |
| Radicular Pain NRS Basic | 8.5±3.0 | 9.5±0.8 | 0.583 |
| Radicular Pain NRS 24h | 6.9±2.5 | 6.2±3.5 | 0.495 |
| Radicular Pain NRS 1month | 4.1±2.6 | 3.2±2.3 | 0.355 |
| Radicular Pain NRS 3month | 3.8±3.0 | 3.5±3.2 | 0.429 |

Note: NRS: Numerical Rating scale, h: hour, data showed as mean ± standard deviation

**Table 2- The mean and standard deviation of disability severity (criteria of Ozone and TF questionnaire score) after treatment in patients participating in the study under transforaminal epidural steroid injection with and without ozone**

| Group | Time | P (Repeated measures ANOVA) |
|---|---|---|

| | 24 hours | First month | Third month | | | |
|---|---|---|---|---|---|---|
| | | | | Time | Time ×group | Group |
| A | 22.5± 10.8 | 19.4 ±7.8 | 17.4±7.3 | 0.089 | 0.071 | 0.862 |
| B | 18.9±15.2 | 7.9±5.4 | 13.5 ±8.7 | | | |
| P (t-test) | 0.401 | 0.001 | 0.137 | | | |

## Discussion

In the present study, transforaminal steroid injection caused a significant reduction in radicular pain in the participants, but adding ozone to steroid did not have a significant effect on the reduction of radicular pain. In line with the results of the present study, in the research conducted by Ryska et al [19], regarding the short-term and long-term effectiveness of radiofrequency pulse, transforaminal injection of oxygen-ozone therapy and epidural steroid injection to relieve pain and improve disability based on the ODI in patients with unilateral chronic radicular syndrome at L5 or S1 who had not responded to conservative treatment, no significant difference was observed among these three groups in terms of pain scores in the third and sixth months and in a descriptive study conducted by Munir et al [20], in the investigation of the results of epidural transforaminal steroid injection in patients with lumbar radicular pain, the results of the study showed that the mean of pain score decreased significantly .

In the clinical trial conducted by Fathy et al [21], in comparing the effect of transfeminal steroid injection of magnesium sulfate alone, steroid alone and the combination of steroid with ozone on radicular pain related to the lumbar disc, by examining 135 patients who had symptoms of prolapse lumbar disc, the results of the study showed that two weeks after the

intervention, in all of three groups, the intensity of pain and disability decreased. In the follow-up 1 and 3 months after the treatment, significant improvement was achieved only in the ozone therapy and magnesium sulfate group. In the follow-up 6 months later, only the magnesium sulfate group showed significant improvement [21]. In the present study, steroid injection with and without ozone was investigated on radicular pain, the patients were followed up for a maximum of 3 months, and the sample size of the present study was smaller than Fathy et al.'s study; However, the results of two studies are consistent in terms of the effect of steroid and ozone treatment on reducing radicular pain. In a clinical trial conducted by Krahulik et al [18] in the Czech Republic, the effect of ozone addition and corticosteroid infiltration on radicular pain was investigated and studied on 150 patients who failed to control pain with conservative treatment methods. Patients were divided into three groups of 50 receiving betamethasone, methylprednisolone and ozone therapy. A significant difference was observed among the three groups in terms of reduction in pain score, the highest reduction in pain score was related to betamethasone and the lowest was related to ozone therapy. The best outcome for ozone therapy was spondylitis and herniated disc [18]. In the review study by Costa et al [22] in the review of studies related to the effect of ozone therapy and transforaminal steroid injection, the results indicated that ozone was effective in all studies, but the use of ozone therapy with microdiscectomy was more effective in reducing pain.

Some researchers have also compared ozone injection alone or with placebo, including Ercalic et al [23] in Turkey, who investigate the effectiveness of intradiscal ozone therapy with and without peri foraminal steroid injection in patients with lumbar disc herniation. Also, Sucuoğlu et al [24] in Turkey compared the effect of intravertebral injection of ozone with placebo on pain caused by acute lumbar disc herniation, and the results of the study showed a significant improvement in the pain scores of patients compared to before treatment in both groups. The recovery rate in the ozone therapy group was higher than the placebo group. In the present study, the effect of transforaminal steroid injection combined with ozone and steroid and its effect on radicular pain was investigated that in both treatment groups, a significant decrease in the pain score of the patients was observed compared to before treatment, but between the group receiving ozone and without Ozone was observed no significant difference in radicular pain intensity at 24 hours, 1 month and 3 months after treatment. Although it seems adding ozone to corticosteroids reduces pain, the pain reduction is not significant.

Our study, transforaminal steroid injection improved the disability of patients with radicular pain, but adding ozone to steroid did not have a significant effect on the improvement of disability caused by radicular pain. In line with the results of the Our study, in the conducted research by Ryska et al [19] regarding the short-term and long-term effectiveness of radiofrequency pulse, transforaminal injection of oxygen-ozone therapy and epidural steroid injection on the disability of patients with unilateral chronic radicular syndrome at L5 or S1 who had not responded to conservative treatment, no significant difference was observed between the three groups in terms of disability score in the third and sixth months.

In a double-blind clinical trial conducted by Sucuoğlu et al [24] in Turkey, comparing the effect of intradisc injection of ozone with placebo on pain caused by acute lumbar disc herniation, there was a significant improvement in patient’s disability scores compared to before treatment, was observed in both of groups. The

recovery rate in the ozone therapy group was higher than the placebo group. In the study of Munir et al [20] in Lahore, transforaminal epidural steroid injection in patients with lumbar radicular pain significantly reduced the disability score of the patients. In the clinical trial conducted by Fathy et al [21], comparing the effect of transforaminal injection of magnesium sulfate alone, steroid alone and the combination of steroid with ozone on radicular pain related to lumbar disc, by examining 135 patients who had symptoms of lumbar disc prolapse, the results of the study showed that two weeks after the intervention, pain intensity and disability decreased in all three groups. However, 1 and 3 months later, significant improvement was achieved only in the ozone therapy and magnesium sulfate group. In the follow-up 6 months later, only the magnesium sulfate group showed significant improvement.

In the clinical trial of Sucuoğlu et al [24] in Turkey, comparing paravertebral ozone injection with placebo on pain caused by acute lumbar disc herniation, ozone therapy during 8 sessions significantly reduced the disability score of patients and the study of de Nêuton et al [25] in Brazil, in examining the effect of using ozone with spinal endoscopy on chronic pain following failed surgery, it caused a 44% reduction in the disability index. The amount of pain reduction was significantly higher in patients with predominant non-neuropathic pain.

As can be seen, the method of conducting studies, including the cause of pain, the type of used steroid, the number of ozone therapy sessions, the combination of ozone with steroids or without steroids, the comparison of ozone with steroids or with placebo, and the time of evaluation and follow-up of patients are different; which may explain the conflicting results.

In our study, no significant side effects were observed as a result of transforaminal steroid injection with ozone. Consistent with the findings of our study, the results of clinical trials and conducted review studies regarding transforaminal and epidural ozone therapy in patients with radicular pain, especially in patients with predominant nociceptive pain [25], pain caused by disc herniation [26] and lower back pain [22], have been reported no complications.

## Conclusion

It seems that adding ozone to corticosteroids has an effect in reducing pain, but at least in the study, it has not had a significant effect. Perhaps one of the reasons is the limitation of the sample size in the study, so it is recommended:

1- Future studies should be conducted with a larger sample size.

2- Since no complications due to ozone injection were observed in any of the patients during the study period, it seems that adding ozone with a suitable dose is safe in patients with radicular pain.

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