Randomized Trial

Efficacy of Intradiscal Ozone Therapy with or without Periforaminal Steroid Injection on Lumbar Disc Herniation: A Double-Blinded Controlled Study

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Background: Intradiscal ozone therapy, a minimally invasive technique, is used in patients that do not respond to standard conservative therapies for low back pain due to degenerative disc-induced lumbar disc herniation (LDH). Many studies on clinical efficacy lack a standardized injection method and are limited by inadequate study design.

Objective: This study aimed to determine the efficacy of periforaminal steroid injection together with intradiscal ozone therapy.

Study Design: A prospective, double-blinded, randomized controlled trial.

Setting: A tertiary care center.

Methods: This study was conducted in 65 patients with low back and leg pain caused by LDH. Group 1 received intradiscal ozone therapy (n = 35) and Group 2 received intradiscal ozone therapy with periforaminal steroid injection (n = 30). Patients were evaluated for pain using the visual analogue scale (VAS), for disability using Oswestry Disability Index (ODI), and for quality of life using the short form 36 health survey administered pre-injection and at one and 6 months post-injection. All procedures were performed under sterile conditions using C-arm fluoroscopy.

Results: Significant improvements were observed in pain, disability, and quality of life in both groups post-treatment compared to pre-injection. Mean pre-injection VAS was not significantly different between the groups (VAS: 7.8 ± 1.1 for Group 1, 7.8 ± 1.2 for Group 2). VAS values at 6 months for Group 1 and Group 2 were as follows: 3.6 ± 2.4, 4.1 ± 1.6, respectively) ($P < 0.001$). Mean pre-injection ODI was not significantly different between the groups (ODI: 20.9 ± 9.6 for Group 1, 25.2 ± 10.3 for Group 2). ODI values at 6 months for Group 1 and Group 2 were as follows: 12.8 ± 9.2, 14.3 ± 7.2, respectively) ($P < 0.001$). However, there were no significant differences between the groups. Similarly, there was no significant difference between the 2 groups on any of these parameters.

Limitations: A limited number of patients and limited follow-up time.

Conclusion: This study showed that intradiscal ozone injection alone was sufficient to treat low back and leg pain caused by LDH and that periforaminal steroid injection does not provide additional benefit, which is contrary to the literature.

Key words: Low back pain, intradiscal ozone, steroid, lumbar disc herniation, lumbar disc degeneration

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Low back pain, the most common cause of disability in the world, creates a significant personal, social, and financial burden (1-3). According to a review published in 2012, the lifelong prevalence of low back pain and lumbosacral radiculopathy was 38.9% (4) and 3 –5% (5), respectively. Although a majority of patients recover with no or minimal treatment, 37 – 54% of patients may still experience pain a year later (6). While no specific cause of pain has been identified in 60 – 80% of patients, disc degeneration is held responsible in 5 – 15% (7).

Minimally invasive methods can be used to prevent or delay open surgery in patients that do not respond to standard conservative treatments for low back pain due to degenerative disc-induced lumbar disc herniation (LDH). Methods, such as intradiscally applied laser decompression, thermal lesion with radiofrequency, and chemonucleolysis with ozone are intended to decrease the disc volume. Although the clinical results of intradiscal ozone chemonucleolysis are similar to the other decompression methods, it offers added benefits of low side effects and cost ratios (8,9).

Ozone has been used in medicine due to its anti-inflammatory, analgesic, and antiseptic properties. It helps alleviate low back pain caused by LDH by reducing inflammation around the nerve root, and subsequently reduces the disc volume (6). Ozone decreases herniated disc volume by breaking up proteoglycans in the nucleus pulposus, neutralizing the negative charge of sulfate side chains, and reducing water retention (10). Previously conducted studies have shown that ozone therapy can be used before approaching surgery in patients who do not respond to conservative treatment or in circumstances where surgery is not a viable option (11-14). Although there are many studies on the clinical efficacy of intradiscal ozone therapy in low back pain caused by LDH, they lack a standardized injection and have other methodological inadequacies (7). For instance, there is no consensus on the injection method, total gas volume, applied ozone concentration, and/or frequency of injection. Besides, the use of periforaminal steroids and local anesthetics has been recommended by many authors in addition to intradiscal ozone injection (15). Although data from some studies support this view, controlled trials investigating the benefits of periforaminal injections in combination with intradiscal ozone therapy over ozone therapy alone report contradictory results. The aim of this prospective study was to investigate the effects of concomitant injection of periforaminal steroids and local anesthetics to intradiscal ozone therapy in a randomized controlled trial.

Methods

Our study was conducted between August 2018 and October 2018 with 80 patients included and went through a 6-month follow-up period. The study was completed with the data of 65 patients. Ethics committee approval was obtained for the study, and patients were informed about the study in written and oral form.

The prospective randomized, controlled, double-blind study included 80 patients between 18 and 75 years old that had low back/leg pain. While 9 patients didn't come for a control examination, 6 patients were excluded from the study upon request, and the final analyses were performed on 65 patients.

Inclusion criteria were as follows: Patients with a diagnosis of LDH because of degenerative disc disease with anamnesis; clinical examination; and imaging findings indicative of low back and leg pain, persistent pain for at least 3 months that was nonresponsive to conservative treatments, and absence of prior history of spinal surgery. Furthermore, no interventional pain treatment was applied within the last 6 months, and patient needed a pain score greater than 4 on the visual analogue scale (VAS) and protrusion level discopathy at L4–5 or L5–S1 on magnetic resonance imaging.

Exclusion criteria were as follows: Patients with systemic infection and uncontrolled systemic disease; hemorrhagic diathesis; history of lumbar surgery, glucose-6-phosphate dehydrogenase deficiency, pregnancy, progressive motor deficits, and calcified disc; and those who refused to participate in the study.

Patients were randomized into 2 groups. Group 1 received intradiscal ozone therapy and Group 2 received periforaminal steroid and local anesthetic treatments in addition to intradiscal ozone therapy. Randomization was performed using the closed envelope method. Patients were evaluated for pain, functionality, and quality of life pre-injection at one and 6 months post-injection. Pain was assessed by VAS, functionality by Oswestry Disability Index (ODI), and quality of life by the short form 36 health survey questionnaires. The primary outcome was pain intensity, and the secondary outcomes were disability and quality of life scores. The physicians and patients that made the evaluations were blinded to the treatment groups.

Procedure

Povidone iodine has been used in all procedures for sterilization and the patients' vital signs were monitored. Imaging was performed with a C-arm fluoroscopy device (BV Pulsera, Philips Corp., Amsterdam, Netherlands). The patient was placed in the prone position, and the lumbar lordosis was flattened by placing a pillow under the abdomen. The injection site was cleaned in accordance with the asepsis antisepsis guidelines. After the fluoroscopy-related level was determined, the disc was ipsilaterally approached with a 22-gauge 20 cm spinal needle using fluoroscopic anteroposterior-lateral-oblique views and a posterolateral approach. Placement of the needle injection was verified with injection of radio-opaque contrast into the center of the disc. Turkozone Blue S was used as the ozone generator. A 5-mL mixture of O2–O3, containing 40 mg/mL O3, was intradiscally administered. In Group 2, a mixture of dexamethasone (8 mg) and 0.05% bupivacaine (1 mL) was injected into the foraminal area (Fig. 1) (7). All injections were performed by an experienced neurosurgeon. After completing the procedure, patients were monitored for one hour and discharged following a recommendation of 3 days of rest and amoxicillin and clavulanic acid 1000 mg twice daily was given for 5 days postoperatively.

Statistical Analysis

SPSS 15.0 for Windows was used for statistical analysis. Descriptive statistics were expressed as num-

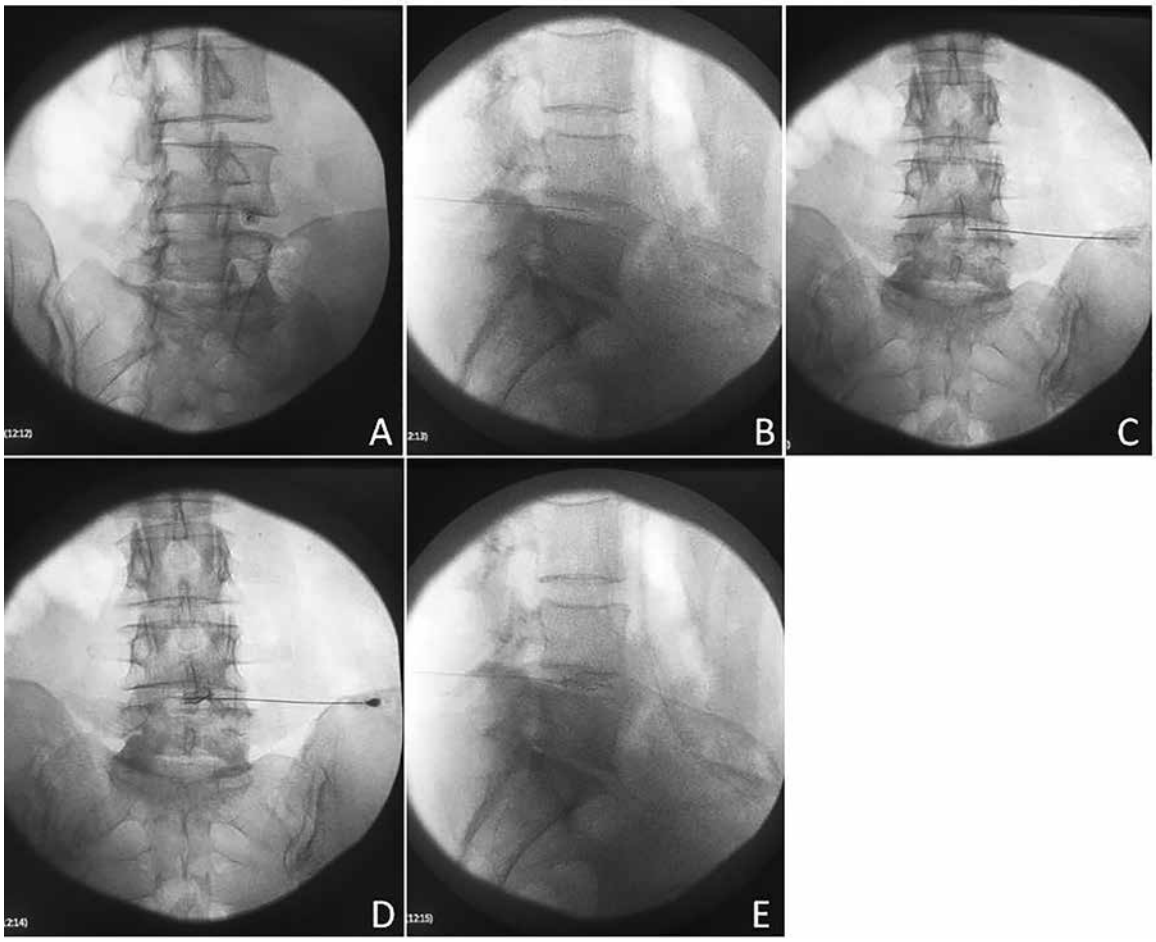

Fig. 1. *Fluoroscopic images of spinal needle inserted in L4-L5 interdiscal space. A) oblique, B) lateral, C) antero-posterior, D) post-contrast antero-posterior, E) post-contrast lateral.*

ber and percentage for categorical variables and as average, standard deviation, minimum, and maximum for numerical variables. Independent variables between the groups were compared using Student's t-test when numerical variables met normal distribution or by Mann–Whitney U test when data were not normally distributed. Dependent variables in more than 2 groups were analyzed using repeated measures analysis of variance when numerical variables were normally distributed and by Friedman analysis when they were not normally distributed. Subgroup analysis was performed using Wilcoxon test and interpreted by Bonferroni correction for nonparametric tests. A *P*-value of less than 0.05 was considered statistically significant.

Results

The mean age of Group 1 was significantly lower than that of Group 2 (P = 0.012). There was no significant difference between the groups in terms of average gender ratios, body mass index (BMI), and duration of pain (Table 1).

Mean pre-injection VAS was not significantly different between the groups. Although VAS values at all post-injection time points were significantly lower than those of pre-injection time point values for both the groups, there was no significant difference between the groups (Tables 2, 3).

Overall, ODI change was statistically significant in both the groups ($P < 0.001$ for both). The mean ODI of Group 1 at one month post-injection was significantly lower than that of Group 2 ($P = 0.003$). There was no statistically significant difference in mean ODI between the groups at 6 months post-injection ($P = 0.301$; Table 2). In Group 1, mean ODI at the first and sixth month post-injection time was significantly lower than those at the preprocedural assessment. There was no significant change in the Group 1 ODI between the first and sixth months. ODI decrease was significant among all

Table 1. *Demographic properties.*

	Group 1		Group 2		*P* value
	Mean ± SD	Min. - Max.	Mean ± SD	Min. - Max.	
Age	41.3 ± 13.1	18-72	49.6 ± 12.2	27-74	0.012
Gender n (%)					
Male	22 (62.9)		14 (46.7)		0.191
Female	13 (37.1)		16 (53.3)		
Height	1.69 ± 0.09	1.55-1.84	1.62 ± 0.15	1.01-1.83	0.083
Weight	78.8 ± 10.4	62-108	75.3 ± 11.6	54-94	0.205
BMI	27.6 ± 2.6	22.2-34.9	27.3 ± 3.7	18.6-34	0.724
Duration of pain (months)	17.8 ± 19.2	1-60	38.1 ± 59.5	1-216	0.382

BMI: body mass index

Table 2. *Pain and disability changes in groups.*

		Group 1	Group 2	*P*
		Mean ± SD	Mean ± SD	
VAS	Preprocedure	7.8 ± 1.1	7.8 ± 1.2	0.857
	1st month	4.6 ± 1.8	5.4 ± 1.8	0.138
	6th month	3.6 ± 2.4	4.1 ± 1.6	0.187
	P	<0.001	<0.001	
ODI	Preprocedure	20.9 ± 9.6	25.2 ± 10.3	0.082
	1st month	12.9 ± 7.6	18.3 ± 8.1	0.003
	6th month	12.8 ± 9.2	14.3 ± 7.2	0.301
	P	<0.001	<0.001	

ODI: Oswestry Disability Index VAS: Visual Analog Scale

Table 3. *VAS and ODI Subgroup Analysis.*

		Group 1	Group 2
		P	*P*
VAS	Preprocedure vs 1st month	<0.001	<0.001
	Preprocedure vs 6th month	<0.001	<0.001
	1st month vs 6th month	0.005	<0.001
ODI	Preprocedure vs 1st month	<0.001	0.001
	Preprocedure vs 6th month	0.001	<0.001
	1st month vs 6th month	0.631	0.014

ODI: Oswestry Disability Index VAS: Visual Analog Scale

Table 4. *Ratios of patients with 50% or more improvement according to VAS.*

		Total		Group 1		Group 2		*P*
		n	%	n	%	n	%	
VAS change pre-1st month	<50%	41	63.1	22	62.9	19	63.3	0.968
	50% or more decrease	24	36.9	13	37.1	11	36.7	
VAS change pre-6th month	<50%	17	28.8	9	29.0	8	28.6	0.969
	50% or more decrease	42	71.2	22	71.0	20	71.4	

VAS: Visual Analog Scale

evaluations in the Group 2 (Table 3). The decrease in pain experienced by the patient due to lumbar disc hernia reflected positively on daily life activities, and hence an improvement in ODI scores.

Patient ratios, with greater than or equal to 50% decrease in VAS values, in the pre- versus post-injection evaluations were not significantly different between the groups (P = 0.968, P = 0.969, at one month post-injection, and P months post-injection, respectively) (Table 4).

The parameters of the quality of life, based on preprocedural evaluations, were not significantly different between the groups. Although there were significant improvements in many subgroup scores in the postprocedural evaluations than those scores in preprocedural evaluations, there were no significant differences between the groups (Table 5).

Discussion

Intradiscal O2–O3 disc chemonucleolysis is being increasingly applied, particularly in European countries, as one of the minimally invasive interventional techniques that produce satisfactory results in low back and leg pain caused by LDH. Radicular pain caused by LDH is attributed to both mechanical and biochemical factors (6). Consequently, intradiscal ozone injection may alleviate low back pain caused by LDH by reducing mechanical compression and by acting on biochemical mechanisms. Proposed mechanisms of action of ozone therapy include interruption of the inflammatory prostaglandin cascade, prevention of tissue hypoxia by increase in O2 concentration, repair of damaged disc by activation of fibroblastic cells, and most importantly reduction in disc volume by preventing water retention and reducing mechanical compression (15). Although several studies have demonstrated the efficacy of intradiscal ozone therapy in treating low back and leg pain caused by LDH (10,13,15,16), a recent meta-analysis (7) has shown that the treatment warrants further investigation given the methodological inadequacies of previous efficacy studies. This underscores the need for well-designed efficacy studies, standardization of the method of injection, the dose and volume to be applied, and patient selection (7,17,18). Studies published in the literature employ different techniques, such as intradiscal O2–O3 injection, foraminal ozone injection, and combination therapy with foraminal steroids (12,13,19). A review published in 2017 (15) recommended injection of a mixture of steroids and local anesthetics to the nerve root area, a suggestion that was echoed by several other studies. Although this approach seemed logical considering the mechanism of low back pain caused by LDH, it has not been adequately supported by controlled studies.

In this study, we investigated the effect of periforaminal steroid and local anesthetic combination concomitantly administered with intradiscal ozone therapy on clinical outcomes in a controlled trial. Our primary outcome measure of mean VAS scores was not significantly different between the groups. Similarly, patient ratios calculated based on VAS and indicating 50% or more pain reduction were also not significantly different between the groups. For the patients whom we couldn't achieve more than 50% of improvement, we believe that we gained these results due to the evaluation of the treatment success with the change in pain, but not with other factors such as the sociocultural environment, pain beliefs, pain behaviors, and psychological factors, which may affect patients' pain, especially chronic pain. Therefore, even though we performed the injection to the source of the pain, we may not have been able to obtain or evaluate the clinically significant response we desired. We believe that further studies evaluating these variables will contribute to the literature. Conflicting results have been reported in previous 2 studies that investigated foraminal steroid injection in combination with intradiscal and foraminal ozone therapy. While Andreula et al (11) demonstrated better results 6 months post-treatment with combination therapy, the study by Zhang et al (19) did not

Table 5. *Changes in quality of life SF-36.*

		Group 1	Group 2	*P*
		Mean ± SD	Mean ± SD	
Physical Function	Preprocedure	48.6 ± 23.5	39.0 ± 21.1	0.091
	1st month	63.9 ± 15.9	49.3 ± 18.6	0.001
	6th month	64.2 ± 19.2	57.5 ± 17.8	0.193
	P	0.002	0.002	
Social Function	Preprocedure	51.8 ± 15.5	53.3 ± 16.1	0.826
	1st month	60.4 ± 18.1	55.0 ± 21.4	0.278
	6th month	46.5 ± 15.1	50.4 ± 12.9	0.332
	P	0.007	0.590	
Mental Health	Preprocedure	59.2 ± 13.1	56.8 ± 14.6	0.680
	1st month	52.0 ± 17.7	56.0 ± 17.2	0.479
	6th month	57.0 ± 18.3	61.6 ± 10.2	0.257
	P	0.265	0.056	
Vitality	Preprocedure	55.1 ± 14.5	51.7 ± 15.2	0.525
	1st month	43.4 ± 17.8	41.5 ± 16.0	0.650
	6th month	53.2 ± 16.1	56.1 ± 10.7	0.422
	P	0.016	<0.001	
Pain	Preprocedure	68.3 ± 20.5	75.8 ± 18.6	0.126
	1st month	51.3 ± 21.3	41.4 ± 17.8	0.050
	6th month	51.5 ± 21.5	54.4 ± 18.6	0.531
	P	0.017	<0.001	
Overall Health	Preprocedure	56.9 ± 13.3	54.3 ± 11.1	0.589
	1st month	49.1 ± 15.9	40.3 ± 17.0	0.036
	6th month	46.0 ± 16.2	54.1 ± 9.4	0.048
	P	0.021	0.001	

SF-36: Short Form-36

find additional benefits with steroids and claimed that ozone alone was sufficient in alleviating the pain. Contradictory results in these 2 studies may be because of the differences in the ozone volume or concentrations or the steroid types applied to the disc and foramen. Additionally, periforaminal ozone injection limited evaluation of the efficacy of steroid injection alone. In other studies investigating combination therapies, periforaminal steroid treatment with or without intradiscal injection of ozone were compared and better results were reported with the addition of intradiscal ozone (20). Another study also reported better results with intradiscal ozone and intraforaminal steroid injection (13). Despite the methodological differences in these 2 studies, they supported combination therapy of ozone and steroid. Our study, investigating the addition of periforaminal steroids to intradiscal ozone therapy, is made up of a design that has never been applied before. However, the fact that we obtained similar VAS changes in both the groups suggests that intradiscal ozone alone is sufficient, which is contrary to the combination therapies recommended in the literature. The study by Bonetti et al (12) detected no difference in efficacy between foraminal ozone alone and combination of foraminal steroid and ozone injection in 306 patients, indicating that the anti-inflammatory effect of ozone gas is as effective as steroid and lasts for a longer duration. Our study, showing that intradiscal injection of ozone gas alone is sufficient in mediating pain relief, supports its use in specific patient populations. This is

particularly true in elderly patients with comorbidities and who cannot use steroids, owing to their possible side effects and additional complications of foraminal injection.

Because of its nonparticulate nature, dexamethasone was the steroid of choice in this study to ensure minimal risk of complications. Reports in the literature indicate that particulate steroids are often responsible for complications following foraminal and epidural injections. Therefore, nonparticulate steroids are recommended as the primary choice for these injections (21). Conversely, some publications also report that particulate steroids are far more effective than nonparticulate steroids (22). A possible reason for the lack of additional benefits with steroid injection in our study may be the use of a nonparticulate steroid instead of more effective particulate steroids. This possibility should be investigated in future studies.

In this study, we evaluated disability and quality of life in addition to pain intensity. Significant improvements were observed in both the groups for disability scores measured by ODI. Although there was a significant improvement in average scores in the ozone group at one month post-injection, this difference disappeared at 6 months. Similarly, there were no significant differences between the groups in terms of quality of life parameters. Previously published studies also assessed disability using ODI. Similar to our study, they reported positive effects of intradiscal ozone therapy on disability (9,23,24). In addition, our study found a positive effect of ozone therapy on quality of life, but no difference between the 2 groups was observed. Other studies in the literature have not evaluated the effects on quality of life.

The design of this study was not primarily aimed at assessing the efficacy of ozone therapy. However, we did observe positive effects on pain, disability, and VAS values. Indeed, success rates of up to 70% (as evaluated by VAS) were detected 6 months post-treatment. These are in accordance with rates reported in the literature. However, a placebo group was not established as the control because the primary aim of this study was not to assess the efficacy.

Finally, there are some limitations to our study. Of these, a limited number of patients and limited follow-up time of 6 months are the most important. In addition, this study cannot predict the efficacy of other particulate steroids. The strength of our study is that it is the first study to investigate the addition of periforaminal steroid injection to intradiscal ozone therapy in patients with radicular pain caused by LDH. In addition, evaluating the effect of this treatment on improving the quality of life in patients is also a powerful feature of this study.

Conclusion

In this study, we investigated the efficacy of periforaminal steroid and local anesthetic in combination with intradiscal ozone therapy. No additional benefit of steroid addition was observed. Our findings suggested that intradiscal ozone therapy alone was sufficient in alleviating low back and leg pain caused by LDH. Although this result does not support the combined injection suggested in the literature, we emphasize the need for more controlled studies on these and other procedural factors.

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Declaration of conflicting interests

Authors declare they have no conflict of interest.

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