

How Effective is Ozone Therapy in Treatment of Lumbar Disc Disease: a Systematic Review of Prospective Studies

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ABSTRACT

Objective: With numerous studies reporting on the clinical efficacy of ozone therapy, there has been a growing interest in its use for disc herniation in lumbar disc disease. The aim of this meta-analysis is to explore the results of the prospective studies using ozone for the treatment of lumbar disc disease.

Methods: Online electronic databases of PubMed, Embase and Scopus were searched using relevant keywords. This review included prospective studies on the treatment of lumbar disc herniation using ozone therapy.

Results: A mean improvement of 4.25 (95% CI 2.93–5.58) in visual analogue scale (VAS) scores was noted. A mean improvement of 20.57 (95% CI 18.47–22.68) in Oswestry disability index (ODI) was noted across the studies on meta-analysis. Meta-regression of the pre-operative and post-operative VAS score did not show any significant association with age at procedure, gender or the level of lumbar disc disease. None of the selected studies reported any minor or major complication.

Conclusion: Ozone treatment in low back pain associated with herniated disc is an effective therapy and can be considered as a standard treatment in cases which failed for conservative treatment. Ozone therapy is a simple method and can be effectively delivered with minimal adverse effects. However, additional

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meta-analysis with high quality randomised controls can be done to further strengthen the evidence for this mode of treatment.

Keywords: ozone therapy, lumbar disc disease, low back pain, lumbar disc herniation, lumbar disc prolapse.

INTRODUCTION

Herniated intervertebral disc has been defined as localized displacement of nucleus, cartilage, fragmented apophyseal bone or annular tissue beyond the disc space and are the most common reason for an orthopedic or neurosurgery consultation (1). Lumbar disc herniation is one of the commonest causes of lower limb radiculopathy for which spine surgery is frequently indicated and is one of the frequently performed surgeries by spine surgeons worldwide. The rate of revision surgeries is estimated to be up to 9% at two years and up to 25% at 10 years, pointing towards the fact that scarring around the epidural space is one of the risk factors for recurrent radiculopathy (2). Hence, a complete and honest trial of conservative treatment is exploited before proceeding to surgery. Activity modification, analgesics, physical therapy and occupational therapy form the overall components of a conservative treatment regimen. Patients who do not obtain relief after a period of four to six weeks can be offered various minimally invasive options like steroid injections into the epidural space. Even after steroid injections, 25 to 72% of patients are indicated for surgery within two years (3, 4). Even though the literature has suggested an improvement in radicular pain, affected patients required multiple injections and had overall limited clinical benefit (5). As a middle path between conservative and surgical care, ozone therapy is postulated as another minimally invasive option based on intradiscal administration, which acts by cleavage of proteoglycans and neutralization of the sulfate side chains, thus diminishing the water retaining capacity of the disc and subsequently its volume (6).

With numerous studies reporting on the clinical efficacy of ozone therapy, there has been a growing interest in its use for disc herniation in lumbar disc disease. The aim of this meta-analysis

is to analyze the results of the prospective studies using ozone for the treatment of lumbar disc disease. □

MATERIAL AND METHODS

Study details

The study was done as per the Preferred Reporting Items for Systematic reviews and Meta Analysis (PRISMA) and the protocol was submitted to PROSPERO (CRD431157). An online search of PubMed, Embase and Scopus was conducted by two authors (SB, VR) using the following keywords: “lumbar disc prolapse”, “lumbar disc herniation”, “lumbar radiculopathy”, “lumbar disc degeneration” and “lumbar disc extrusion”. “Ozone” and “ozone-oxygen” were the search terms used for the intervention. Boolean operators were appropriately used in PubMed. Search guidelines for Embase and Scopus were followed. The search results were exported to spreadsheets (Microsoft Excel, USA). Duplicates were removed by using the “Duplicate Removal” function of the spreadsheet software. After initial screening of titles and abstracts, full text articles of the remaining selection were explored for final eligibility. Any disagreement was resolved by the intervention of the two senior authors (VK, AJV).

Eligibility criteria

This review included studies on the treatment of lumbar disc herniation by ozone therapy. Only prospective studies with or without randomisation and those which reported pain scores and ODI scores or MacNab outcome scores were included. Also, only studies administering isolated intradiscal ozone therapy were included. No filter was set on the language and follow-up period. Isolated single case reports were excluded. Studies with intramuscular ozone were excluded. Non-randomised clinical trials, observational studies, retrospective studies, review articles, commentaries, editorials, conference presen-

tations, operative techniques and articles with no available full text were excluded from this review. Screening of the bibliography of the included studies as well as previous reviews was done. Any dispute regarding inclusion was resolved by the senior authors (VK, AJV).

Quality assessment

The eight eligible studies were assessed for their study quality using appropriate tools. There were four randomised studies which were assessed using ROB2 (5, 7, 9, 10), one of the numerous tools proposed for Cochrane authors and editors to assess the risk of bias in randomised trials. It comprises five sets of prefixed domains of bias, including: 1) randomisation process; 2) deviations from intended interventions; 3) missing outcome data; 4) measurement of outcomes; and 5) selection of reported results which focus on the different aspects of the trial design, conduct and reporting. Each domain has a set of questions which are to be answered as yes, probably yes, probably no, no or no information. The risk of bias is calculated based on the responses. The options "yes" and "probably yes" have the same implication (positive response) as the options "no" and "probably no" (negative response), whereas the option "no information" is exercised when details about the question asked are missing. Different templates of the ROB2 tool are available to suit the study design which may be 1) randomised controlled trials (RCTs) with parallel groups; 2) cluster randomised parallel group trials; and 3) crossover RCTs.

Four prospective comparative studies were included in the present review (11-14) and their quality was assessed using the methodological index for non-randomised studies (MINORS) (15). MINORS has a list of 12 items which have to be answered in terms of numbers 0 (no information available/not reported), 1 (reported but inadequate data) and 2 (reported with adequate data). The first eight items are valid for all non-randomised studies, while the last four items are useful for comparative studies only. The maximum score can be 16 for non-randomised studies with no comparison and 24 for non-randomised comparative study designs. The final quality of the study is obtained in the form of a ratio. The tool has been successfully used and recommended over the years.

Data extraction

A pre-decided spreadsheet was prepared after full text analysis of the included studies by the senior authors (VK, AJV), followed by data extraction by one author (SI). Two authors (SB, VR) ensured the adequacy of collected data. Mean, ranges, standard deviation (SD) and confidence intervals of the outcomes were sought. Demographic data in the form of study size, age at surgery, gender of the study participants, duration of symptoms, previous treatment, follow-up period and study group were all recorded. The pre-intervention and post-intervention data regarding pain and quality of life scores were obtained to synthesise evidence. Any adverse event in either group was also noted.

Statistical analysis

Mean, SD and ranges were used to describe the collected data. Open Meta Analyst (Brown University, USA version 13) with a random-effect model was used for meta-analysis. A formal meta-analysis was done using the Der Simonian and Laird method and the outcome was reported as mean difference (MD). The correction of preoperative and postoperative pain scores was used for comparison. The I² statistic was used to assess the heterogeneity. A p value of < 0.5 was considered statistically significant for the overall effect Z test. Low, moderate and high level of heterogeneity was denoted as per I² values of 25%, 50% and 75%, respectively. Sensitivity analysis of the meta-analysis was aimed at identifying any study contributing to heterogeneity. Narrative review of data that could not be statistically analysed was done. ▣

RESULTS

Literature search

The inclusion and exclusion criteria were applied and data was extracted from PubMed and Scopus databases. There were 343 articles retrieved with the keywords used in various combinations. After duplicate removal and application of study criteria, 29 reports were sought for full retrieval. Of these, 21 studies were excluded because they did not report any objective criteria to assess the outcomes (n=17) or were radiological studies (n=4). There were eight eligible full-length articles, out of which four were prospective randomised studies and the remain-

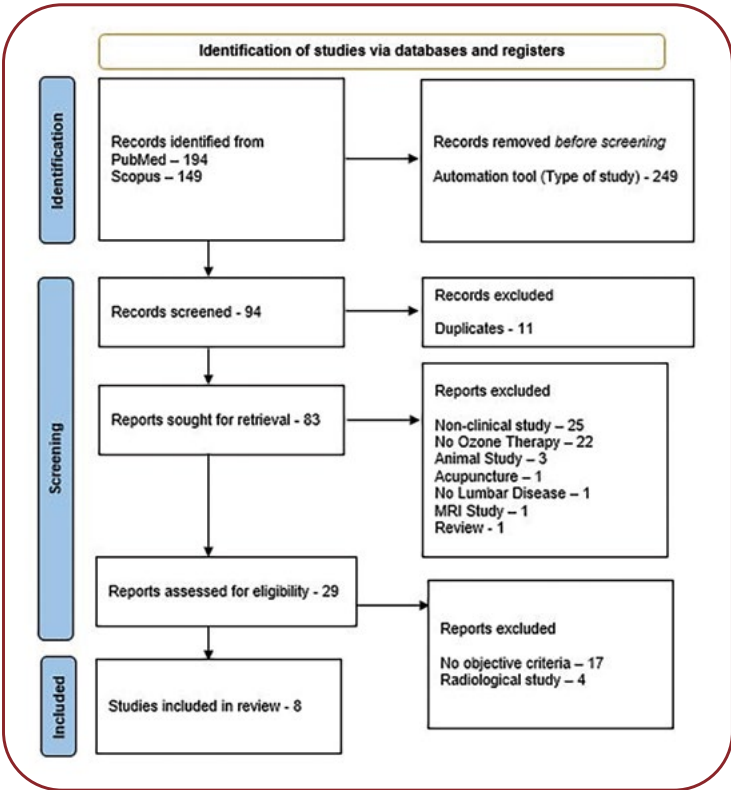


FIGURE 1. PRISMA flowchart depicting the methodology of the study.

Study ID	Experimental	Comparator	Outcome	Weight	D1	D2	D3	D4	D5	Overall
Kelekis et al (2022)	Ozone therapy	microdiscectomy	improvement in radicular pain in terms of NRS and RMDI	1	+	+	+	+	+	+
Elawamy et al (2018)	Ozone 10 ml (40ug/ml)	Ozone 10 ml (30ug/ml)	pain relief in terms of VAS and ODI	1	+	+	+	+	+	+
Rahimzadeh et al (2018)	Ozone therapy	Laser disc decompression	Pain relief in terms of ODI	1	+	+	+	+	+	+
Gautam et al (2010)	Ozone therapy	Radiofrequency ablation	Pain relief in terms of VAS and ODI	1	+	+	+	+	+	+

+

Low risk

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Some concerns

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High risk

D1Randomisation process

D2Deviations from the intended interventions

D3Missing outcome data

D4Measurement of the outcome

D5Selection of the reported result

FIGURE 2. Quality assessment of randomised studies using the ROB2 tool

Study No.	Study authors, year of publication	A clearly stated aim	Inclusion of consecutive patients	Prospective collection of data	Endpoints appropriate to the aim of the study	Unbiased assessment of the study endpoint	Follow-up period appropriate to the aim of the study	Loss to follow up less than 5%	Prospective calculation of the study size	An adequate control group	Contemporary groups	Baseline equivalence of groups	Adequate statistical analyses	Total score
1	Yang et al (2022)	2	1	2	2	0	2	2	0	2	2	2	2	19/24
2	Hosseini et al (2018)	2	2	2	2	0	2	2	0	NA	NA	NA	NA	12/16
3	Ezeldin et al (2018)	2	1	2	2	0	2	2	0	NA	NA	NA	NA	11/16
4	Buric et al (2005)	0	1	2	2	0	2	2	0	NA	NA	NA	NA	9/16

TABLE 1. Quality assessment of non-randomised studies by the methodological item for non-randomized studies (MINORS) tool

TABLE 2. Demographic data of studies included in the present study

Study	N	Type of study	Age at procedure	Level of intervention	Gender (male/female)	Pre-procedure VAS	Post-procedure VAS	Pre-procedure ODI	Post-procedure ODI	Follow-up (months)	Complications
Kelekis <i>et al</i> (2022)	24	Prospective randomized study	39.5±10.5	L4-S1=11 L5-S1=13	17/7	7.6±1.08	3.09±0.55	RMD (values only graph given)		6	Nil
Yang <i>et al</i> (2022)	60	Prospective randomized study	52.31±5.82	L3-L4=24 L4-L5=28 L5-S1=8	31/29						Nil
Rahimzadeh P <i>et al</i> (2018)	20	Prospective randomized study				7.9	3	62.7	25.1	12	Nil
Elawamy <i>et al</i> (2018) (1)	30	Prospective randomized study	40.7±10.7		16/14	8.3±0.18	1.7±0.24	37±0.8	12±0.7	12	Nil
Elawamy <i>et al</i> (2018) (2)	30	Prospective randomized study	39.7±9.2		11/19	8.2±0.18	1.76±0.24	38±0.7	12±0.7	12	Nil
Ezeldin <i>et al</i> (2018)	50	Prospective non randomized study	54.5±12.9		25/25	2.38±0.90	1.04±0.92	35±14.36	19.36±13.12	12	Nil
Hosseini <i>et al</i> (2018)	128	Prospective non randomized study	40.1±10.7		60/68	7.5±0.8	5±1.4	48.4±9.6	34.4±12.4	-	Nil
Gautam <i>et al</i> (2011)	41	Prospective randomized study	43.5±9.9	L4-L5=9 L5-S1=14 L3-L4 & L4-L5=6 L4-L5 & L5-S1=12	27/14	7.27±1.01	3.31±1.29	45.5±10.3	25.5±11.3	12	Nil
Buric <i>et al</i> (2005)	30	Prospective non randomized study	45±14.2		16/14	5.3±2.2	0.9±1.0	20.8±17.86	17.04±17.5	12	Nil

VAS=visual analogue score; ODI=Oswestry disability index; RMD=Roland-Morris disability questionnaire

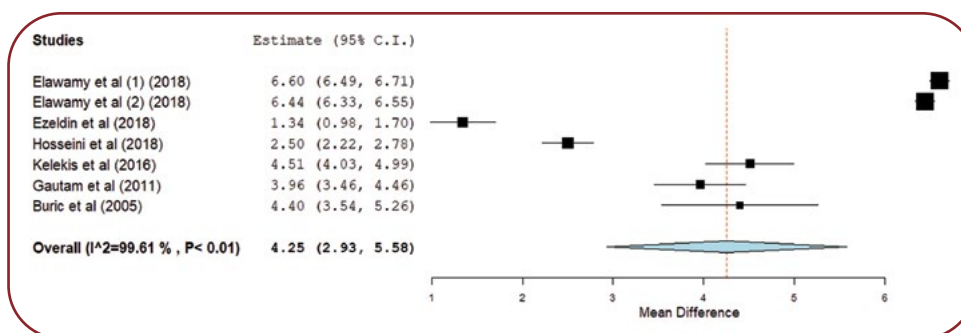


FIGURE 3. Forest plot depicting the significant improvement in VAS scores

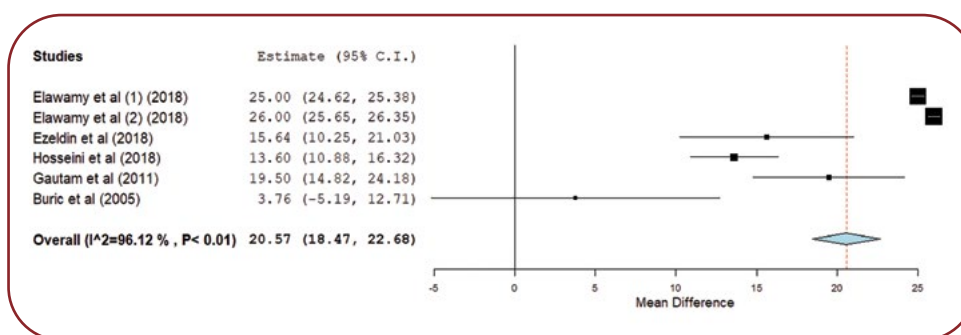


FIGURE 4. Forest plot depicting the significant improvement in ODI scores

assessment of the study endpoint or prospective calculation of the study size (11-14).

There was a high degree of heterogeneity among studies with I² value of more than 90% ($p<0.05$). Sensitivity analysis revealed that all explored studies had significantly contributed to the heterogeneity. Funnel plot of studies inclu-

ded in the quantitative analysis did not reveal any publication bias.

Demographic data

The eight included studies totalized 413 patients, among whom 203 were males and 190 females (Table 2). Rahimzadeh *et al* did not specify the

sex distribution in his study (7). All included studies, except that conducted by Kelekis *et al*, had a minimum follow-up of 12 months (5). The majority of patients had ozone administration at L4-L5 level and the second most common vertebral level involved was L5-S1.

Outcomes and complications

Six studies reported on the preoperative and postoperative VAS scores (5, 9, 10, 12-14). A mean improvement of 4.25 (95% CI 2.93–5.58, $p < 0.05$) in VAS scores was noted (Figure 3). Similarly, five studies reported their outcomes based on ODI (9, 10, 12-14). A mean improvement of 20.57 (95% CI 18.47–22.68, $p < 0.05$) was noted across studies on meta-analysis (Figure 4). None of the studies reported any minor or major complication. Meta-regression of the preoperative and postoperative VAS scores did not show any significant association with age at procedure, gender or the level of lumbar disc disease. □

DISCUSSION

Ozone therapy in chronic back pain is an established modality of treatment (9). This systematic review was done to assess the clinical outcomes and adverse effects associated with ozone administration in chronic back pain. The majority of articles included in this review showed a significant improvement in chronic back ache with almost no adverse events. Few articles also compared the clinical outcomes with standardised treatments in chronic back pain like microdiscectomies and found a similar improvement with ozone treatment alone. These results are in accordance with a previous systematic review done in 2018 (16). We followed a stringent inclusion criterion to select only articles reporting on prospective randomised controlled studies or at least prospective studies without randomisation. This is the reason why we had only eight studies in the final qualitative data synthesis, which helps to improve the overall evidence of the systematic review.

The majority of articles used clinical outcomes like VAS and ODI scores to see the improvement, except for one article which used the RMDQ. Some of the articles in our review compared the clinical outcomes of ozone treatment with gold standard procedures. Kelekis *A et al* compared microdiscectomy to ozone treat-

ment in randomly allocated patients and found that ozone treatment was non inferior to microdiscectomy in the treatment of herniated intervertebral disc pathology (5). Gautam S *et al* explored and compared ozone therapy with percutaneous intradiscal radiofrequency thermocoagulation (PIRFT) administered at 80 degrees C for 360 seconds to randomly allocated patients; the study group concluded that a combination of Ozone-PIRFT was more efficacious in reducing pain scores and analgesic consumption when compared to ozone alone in contained herniated disc patients (10). Yang Y *et al* compared ozone therapy with ozone in combination of betamethasone around the nerve root (11) and focussed on noting the improvement in range of motion of lumbar spine following both therapies; they concluded that a combination therapy including steroid and ozone resulted in higher benefits when compared to plain ozone treatment.

Ozone acts by causing an oxidative effect causing downregulation of many inflammatory mediators such as interleukin-1 beta, tumour necrosis factor-alpha, etc (17). This oxidative effect is dose-related and varies with the strength of administered ozone gas. At concentrations of 40-70 micrograms, ozone exerts a tissue destruction effect and at concentrations of 20-30 micrograms the immune system is regulated. At very low concentrations of less than 20 micrograms, ozone improves microcirculation (9). Elawamy *et al* studied these concentrations of ozone in back pain and evaluated the quality of pain relief following administration of different concentrations of ozone (9). They used two concentrations (*i.e.*, 40 micrograms and 30 micrograms) in two groups of patients who were randomly divided. They also studied the reduction in disc height following the procedure and the relation of the reduction in disc height to the clinical parameters of VAS and ODI scores. The study group concluded that there were highly significant negative correlations between disc height reduction percentage and VAS score at the end of six months. However, no difference in the dosage of ozone therapy was seen between the two groups. It is a point to be noted that in all included articles, none of them elaborated about adverse events during their study period. The studies in the literature have demonstrated subtle adverse effects following ozone therapy like

insomnia, itching, gastritis, tachycardia and hot flushes (18, 19). By far, ozone treatment is a relatively safe procedure, which is shown by the articles selected for the present review.

The strength of our study is the fact that all eligible articles were prospective studies, half of which being prospective and randomised studies. There are also some limitations because quantitative analysis could not be performed due to heterogenic data which could not be compared across all studies, and also the quality of the included studies is questionable. □

CONCLUSIONS

Ozone treatment in low back pain associated with herniated disc is an effective therapy and can be considered a standard treatment for patients in whom conservative treatment failed. Ozone therapy is a simple method and can be

effectively delivered with minimal adverse effects. However additional meta-analysis with high quality randomised controls can be done to further strengthen the evidence for this modality of treatment. □

Conflicts of interest: none declared.

Financial support: none declared.

Data availability: The datasets generated during this review shall be available upon reasonable request to the corresponding author.

Authors' contribution: VK – concept, design, manuscript editing and review; SI – literature search, data acquisition and analysis, manuscript preparation; VR – data acquisition, data analysis, statistical analysis; SRV – data analysis, statistical analysis; AJ – data acquisition, data analysis; AV – concept, design, manuscript editing and review; SB – manuscript preparation, editing and review.

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