MAEDICA – a Journal of Clinical Medicine
2025; 20(1): 137-139
https://doi.org/10.26574/maedica.2025.20.1.137

MÆDICA - a Journal of Clinical Medicine

LETTERS TO THE EDITOR

Ozone Therapy for Lumbar Disc Disease. Some Comments

Salvatore CHIRUMBOLO[a], Luigi VALDENASSI[b], Francesco VAIANO[b], Umberto TIRELLI[c], Tommaso RICHELMI[b], Marianno FRANZINI[b]

[a]Department of Engineering for Innovation Medicine, University of Verona, Verona, Italy

[b]Italian Scientific Society of Oxygen-Ozone Therapy (SIOOT) and High Master School in Oxygen-Ozone Therapy, University of Pavia, Pavia, Italy

[c]Tirelli Medical Group, Pordenone, Italy

TO THE EDITOR:

The systematic review on ozone therapy for lumbar disc disease presents a structured and well-documented approach to assessing the treatment's efficacy. However, several weaknesses, biases and methodological flaws undermine the strength of its conclusions. One of the major concerns is the significant heterogeneity among the included studies, which is acknowledged in the results section but not adequately addressed in the discussion section (1).

The I^2 value exceeding 90% indicates that the variability between studies is extreme, making it difficult to draw reliable conclusions from the meta-analysis. Although a sensitivity analysis was conducted, it failed to identify a single source of heterogeneity, suggesting that multiple confounders were present in the data. The authors did not discuss potential strategies to mitigate this heterogeneity, such as subgroup analyses based on patient characteristics, different ozone administration techniques, or variations in follow-up periods (1).

Another major flaw is the lack of comprehensive assessment of adverse effects. The review states that none of the included studies reported minor or major complications, which is highly suspicious given that ozone therapy, like any medical intervention, carries inherent risks. While the discussion briefly mentions possible side effects found in the previous literature, such as insomnia, itching, gastritis, tachycardia and hot flushes, none of these were reported in the selected studies. This raises concerns about reporting bias or inadequate follow-up procedures in primary studies. Moreover, given that ozone therapy is still considered controversial in some medical communities, the absence of a critical discussion on its safety profile weakens the credibility of the review.

The literature search strategy also has limitations. Although the authors followed PRISMA

Address for correspondence:
Prof Salvatore Chirumbolo, PhD
Department of Engineering for Innovation Medicine, University of Verona, Italy
Postal address: Strada Le Grazie 8, 37134 Verona, Italy
Tel. +390458027645; email salvatore.chirumbolo@univr.it

Article received on the 28th of February 2025 and accepted for publication on the 12th of March 2025

guidelines and registered their protocol with PROSPERO, their search was restricted to PubMed, Embase and Scopus. The exclusion of other databases, such as Cochrane Library or Web of Science, may have led to selection bias. Furthermore, no grey literature or unpublished data were considered, which could have introduced publication bias. The review acknowledges that a funnel plot did not reveal any significant publication bias, but given the small number of studies included (eight in total), the statistical power of such an analysis is limited. The decision to exclude retrospective studies and non-randomized observational data, while justified for ensuring study quality, may have resulted in the omission of valuable real-world data on ozone therapy's effectiveness and safety (1).

The methodological quality of the included studies is another concern. While the review claims that randomized controlled trials (RCTs) had a low risk of bias according to the ROB2 tool, it does not provide a detailed breakdown of individual study biases. For example, whether all studies had proper allocation concealment, blinding, or intention-to-treat analyses remains unclear.

The non-randomized studies were assessed using the MINORS tool, but the review does not provide the exact scores for each study, making it difficult for readers to assess their reliability. The statement that none of these studies had an "unbiased assessment of the study endpoint or prospective calculation of the study size" is a red flag, indicating that the findings from these studies may be less robust than suggested.

The statistical analysis is another area where the review falls short. The meta-analysis was conducted using a random-effects model, which is appropriate given the heterogeneity, but no justification is provided for the specific model used (DerSimonian and Laird). The review reports mean differences for VAS and ODI scores but does not discuss whether these differences are clinically meaningful. A statistically significant reduction in pain scores does not necessarily translate to a meaningful improvement in patient quality of life. Furthermore, the lack of a control group in some included studies means that the placebo effect cannot be ruled out. The meta-regression analysis, which found no significant association between treatment efficacy and factors like age, gender, or disc level, is presented without further interpretation. The lack of subgroup analysis means that the review fails to explore whether specific patient populations benefit more from ozone therapy than others.

The conclusions drawn by the authors are overly optimistic and lack nuance. They state that "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." This is a strong claim that is not fully supported by the evidence. Given the high heterogeneity, potential biases and methodological limitations, a more cautious conclusion would have been appropriate. Instead of asserting that ozone therapy can be a standard treatment, the review should have emphasized the need for higher-quality RCTs with standardized protocols and longer follow-ups to confirm its efficacy and safety.

The discussion section fails to address several key points that would have strengthened the review. There is no comparison with alternative treatments such as epidural steroid injections, physiotherapy, or surgical interventions beyond microdiscectomy. Given that many patients with lumbar disc disease experience spontaneous symptom improvement over time, a placebo-controlled design would have been ideal, yet this is not discussed. Additionally, while the proposed mechanism of action of ozone therapy is explained (oxidative degradation of proteoglycans leading to volume reduction), there is no mention of potential long-term consequences, such as accelerated disc degeneration or adjacent segment disease. The review also does not acknowledge the ongoing debate in the medical community about the validity of ozone therapy, which has not been universally accepted in spine care guidelines.

Certain sections of the manuscript contain clumsy or misleading statements. For example, the abstract states that "none of the selected studies reported any minor or major complication", which could be misinterpreted as evidence that ozone therapy is entirely risk-free, rather than a reflection of poor adverse event reporting. The phrase "ozone therapy is a simple method and can be effectively delivered with minimal adverse effects", in the conclusion section, similarly downplays safety concerns. The introduction claims that "ozone therapy is postu-

lated as another minimally invasive option", yet it is later discussed as if its effectiveness is already well-established, creating inconsistency in the argument. The review also states that "there was a high degree of heterogeneity among studies with an I^2 value of more than 90%", but it does not adequately explore the sources of this heterogeneity.

Some oversights in study design and data presentation further weaken the manuscript. The authors present forest plots for VAS and ODI scores but do not provide a table summarizing individual study results, making it difficult to assess variations in outcomes. The review does not mention whether any of the included studies were industry-sponsored, which is an important factor when evaluating potential bias. Additionally, while the review reports that the included studies had an average follow-up of 12 months, it does not discuss whether longer-term outcomes were assessed. Given that lumbar disc disease is a chronic condition, a follow-up of one year may not be sufficient to determine the durability of ozone therapy's effects.

In summary, while the review provides a useful synthesis of available literature on ozone therapy for lumbar disc disease, it is marred by substantial heterogeneity, a lack of critical discussion on adverse effects, and an overly optimistic interpretation of results. The exclusion of retrospective data and grey literature limits the generalizability of its findings, while methodological flaws in the included studies raise concerns about bias. The conclusions are too strong given the available evidence and the review does not sufficiently compare ozone therapy with other established treatments. Future research should focus on high-quality, placebo-controlled RCTs with standardized protocols to provide more definitive answers regarding the efficacy and safety of ozone therapy in lumbar disc disease.

Conflicts of interest: none declared.

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