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Review

Metanalysis on the effectiveness of low back pain treatment with oxygen-ozone mixture: Comparison between image-guided and non-image-guided injection techniques

Gustas Rimeika [a], Luca Saba [b], Ganesan Arthimulam [c], Luigi Della Gatta [d,*], Kristina Davidovic [e], Matteo Bonetti [f], Donatella Franco [g], Camilla Russo [d], Mario Muto [d]

[a] Department of Radiology, Nuclear Medicine and Medical Physics, Vilnius University, Vilnius, Lithuania
[b] Department of Radiology, Azienda Ospedaliera Universitaria di Cagliari-Polo di Monserrato, Cagliari, Italy
[c] Interventional Radiology Unit, Department of Diagnostic Imaging, Kuala Lumpur General Hospital, Malaysia
[d] Department of Neuroradiology, A.O.R.N. Cardarelli, Naples, Italy
[e] Clinical Centre of Serbia, Institute for Radiology, Emergency Room Department, Serbia
[f] Department of Neuroradiology, Istituto Clinico Città di Brescia, Italy
[g] Department of Precision Medicine, University of Campania "Luigi Vanvitelli", Naples, Italy

HIGHLIGHTS

- Low back pain (LBP) is a common spine disease and one of the most frequent causes of absence from work in developed countries.
- In case of conservative approaches failure, minimal invasive techniques can be envisaged as second line therapies in LBP.
- Percutaneous oxygen-ozone injections are one of the most cost-effective procedures.
- Imaging-guided ozone therapy showed higher therapeutic efficacy and lower age-related variability compared to non-image-guided techniques based on anatomical landmarks.

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ABSTRACT

Low back pain (LBP) is a common disorder affecting an increasing number of people worldwide, whose diagnosis is focused on the identification of triggering causes. First line therapy usually starts from conservative approaches, whereas second line treatments include a spectrum of minimally invasive techniques, before resorting to more invasive surgical approaches. Among minimally invasive techniques, percutaneous oxygen-ozone injections represent one of the most common and cost-effective procedures. Aim of this study is to provide a metanalysis on literature evidences on percutaneous oxygen-ozone injections, comparing image-guided to non-image-guided techniques for LBP treatment. Imaging-guided procedures showed better performances compared to non-image-guided techniques based only on anatomical landmarks, with higher therapeutic efficacy and lower age-related variability in clinical results.

1. Introduction

Low back pain (LBP) is a common disorder involving spinal joints, intervertebral disk, vertebral bodies and para-vertebral soft tissues, varying by posture and movement. Sciatica is a specific type of LBP referring to pain radiating down the buttock and leg along the path of sciatic nerve, usually compressed in the setting of spine osteoarthritis. LBP and sciatica affect hundreds millions people worldwide, regardless of age, sex, occupation and lifestyle, with approximately 80% of the population experiencing LBP during their lives [1,2]. Economic and

Abbreviations: BPI, Brief Pain Inventory; CT, Computed Tomography; DSA, Digital Subtraction Angiography; IF, Impact Factor; LBP, Low back pain; LDH, Lumbar Disc Hernia; MRI, Magnetic Resonance Imaging; ODI, Oswestry Disability Index; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines; RMDQ, Roland Morris Disability Questionnaire; US, ultrasonography; VAS, Visual Analogue Scale for pain.

* Correspondence to: Department of Neuroradiology, A.O.R.N. Cardarelli Via A. Cardarelli 9, 80131 Naples, Italy.
E-mail address: luigi.dellagatta@hotmail.it (L. Della Gatta).

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social impact of LBP is therefore impressive, with higher incidence of depression and isolation commonly described in affected people [3,4].

LBP frequently recognize variable and multi-factorial aetiology. Treatment should generally begin with conservative methods (i.e. oral medications, physical therapy, exercise, occupational modifications); second-line treatments include a wide spectrum of minimally invasive techniques, before resorting to a more invasive surgical approach (mandatory in case of neurological deficit, progressive foot droop and paralyzing sciatica). Among minimally invasive techniques, percutaneous oxygen-ozone (O_2-O_3) gaseous mixture injections are one of the most common and effective procedures adopted in case of conservative approach failure. Since the 90′s, oxygen-ozone injections have been administered into the paravertebral muscles, intervertebral discs, facet joints and neural foramina in order to achieve pain resolution [5]. Needle tip positioning at target can be performed either with or without image-guidance based on fluoroscopy, computed tomography (CT) or rarely ultrasonography (US); if necessary, the procedure can be performed with anaesthesiologic support. In non-image guided procedures, the injection of O_2-O_3 mixture is targeted in the muscular paravertebral tissues localized at the level of pathologic intersomatic space. Conversely, image-guided procedures are based on periradicular, intraforaminal or intradiscal injection of O_2-O_3 mixture at the level of the metamer of the herniated disc under image-guidance.

At present, no consensus was reached concerning the gold standard procedure in terms of efficacy, effectiveness, complications risk and stability over time [5]. Aim of this metanalysis is to provide a comparison in terms of efficacy and effectiveness of percutaneous image-guided versus non-image-guided oxygen-ozone injections in the treatment of LBP and sciatica.

2. Methods

Metanalysis was based on retrospective bibliometric search of papers on percutaneous image-guided and non-image-guided oxygen-ozone injections in the treatment of LBP and sciatica published between January 1980 and December 2020, based on data publicly available on National Library of Medicine MEDLINE database. Search syntax used to gather bibliographic data is listed in Table 1; study selection for statistical purposes was performed in accordance to PRISMA guidelines (Fig. 1). Case reports, congress posters/abstracts, animal model studies, reviews/meta-analyses, as well as methodological or ex-vivo researches were not included. Other exclusion criteria were: injections not including oxygen-ozone (i.e. steroid, collagenase, etc.); studies that analysed non-percutaneous ozone injections (i.e. spinal endoscopy, etc.); studies analysing oxygen-ozone injections performed in non-lumbar region; non-Anglophone publications. Papers were further evaluated to identify missing data needed to perform the metanalysis; missing data were extracted by using statistical methods when possible, conversely studies were removed. A total number of 45 published original articles were finally included in the metanalysis; the complete list is available as a table in Supplementary Materials.

Available data from each original article were then divided in two groups based on the type of injection technique: articles describing non-image-guided oxygen-ozone injections (n = 9.20%); articles describing image-guided oxygen-ozone injections, independently from the adopted imaging technique (n = 37.8%). Papers were considered together in the same group independently from the oxygen-ozone gaseous mixture used for injection and pharmacological associations; articles directly comparing image-guided and non-image-guided techniques were considered in both groups separately (n = 1). Data extraction was performed by two neuroradiologists in consensus, with the supervision of an experienced interventional neuroradiologist.

Clinical outcomes included pre- and post-treatment (from 1 to 6 months after treatment) measures such as Visual Analogue Scale for pain (VAS), Oswestry Disability Index (ODI), McNab and modified McNab clinical outcome score, Roland-Morris Disability Questionnaire (RMDQ), and Brief Pain Inventory (BPI); moderators analysis included mean age of treated patients, impact factor (IF) of the publishing journal, and publication year. Whereas VAS, ODI, RMDQ and BPI are referred to continuous variables, for the MacNab score an odds treatment effect was used to allow dichotomous variables to be pooled together with continuous data, as the standard error of the log odds ratio was converted to the standard error of a standardized mean. A logistic regression model with random-effects analysis was then performed by using the free online software ProMeta-Version2, Internovi, Cesena (Italy), and Hedges'*g* for each study was used for effect sizes calculation; the statistic $I2$ has been used to measure heterogeneity. Funnel plot test was also performed to assess potential publication biases due to under-published/under-reported non-significant results, as well as to pipeline, subjective reporting and duplicate reporting errors. Statistic *t*-test to compare mean effect difference between the two procedures was performed by using XLSTAT-Version 2014.5.03. Purely qualitative data concerning side or adverse effects (from both original articles and case reports) were only included in the discussion section and not considered for quantitative analysis.

Table 1
Search syntax used for bibliographic data retrieving on National Library of Medicine MEDLINE database.

MEDLINE
((((((((((((((paraspinal ozone injections) OR (periganglionic ozone injections)) OR (periradicular ozone injections)) OR (chemodiscolysis)) OR (fluoro-guided ozone injections)) OR (CT-guided ozone injections)) OR (image-guided ozone injections)) OR (intramuscular ozone injections)) OR (paravertebral ozone injections)) OR (intradiscal ozone injections)) OR (oxygen ozone spine)) OR (oxygen ozone herniated disc)) OR (oxygen ozone trial)) OR (oxygen ozone infiltration)) OR (ozone injections)) OR (ozone therapy)) AND (spine)

3. Results

In all the 45 articles finally included in the metanalysis, ozone was administered as a gas mixture of O_2-O_3 with a concentration ranging between 10 and 40 μg/mL; O_2-O_3 injection was coupled to steroids in 28.3% cases, anti-inflammatory drugs in 2.2% cases and anaesthetics in 13% cases, whereas in 6.5% cases was coupled to other techniques including radiofrequency thermocoagulation, collagenase injection, bioresonance magnetotherapy and/or electrostimulation. Image-guided techniques were based both on fluoro-guidance (49.5%) or CT-guidance (49.5%), with a single prospective study based on US-guided paravertebral injections (1%); in 14.3% cases O_2-O_3 was only administered at the level of facet joints and periradicular-intraforaminal space, in 22.9% cases at the level of both the periganglionic/intraforaminal space and the herniated disc, whereas in the remaining 60% cases only within the herniated disc. Conversely, non-image-guided techniques were all based on paravertebral-intramuscular injections using anatomic landmarks alone.

The overall treatment effect size shows a mean reduction in pain and pain perception of about − 4.48 in case of image-guided oxygen-ozone injection (95%CI: −5.20 to −3.75; $p < 0.0001$; variance:0.14) (Fig. 2), versus − 3.17 in case of non-image-guided oxygen-ozone injection (95% CI: −4.3 to −2.04; $p < 0.0001$; variance:0.33) (Fig. 3); mean difference in effect size and overall number of collected evidences between the two groups is statistically significant ($p < 0.05$). When analysing the possible impact of moderators, no correlation with patients' mean age was observed for image-guided procedures ($p = 0.5$); conversely a significant correlation between age and treatment efficacy was observed for non-image-guided techniques ($p = 0.009$), with higher pain reduction in younger subjects and worst performance levels in older ones (Fig. 4). At the same time, no correlation with publication year ($p = 0.7$ for image-guided and $p = 0.6$ for non-image-guided techniques, respectively) and journal IF emerged ($p = 0.2$, both for image-guided and non-image-guided techniques). Moreover, $I2$ statistics revealed the presence of a

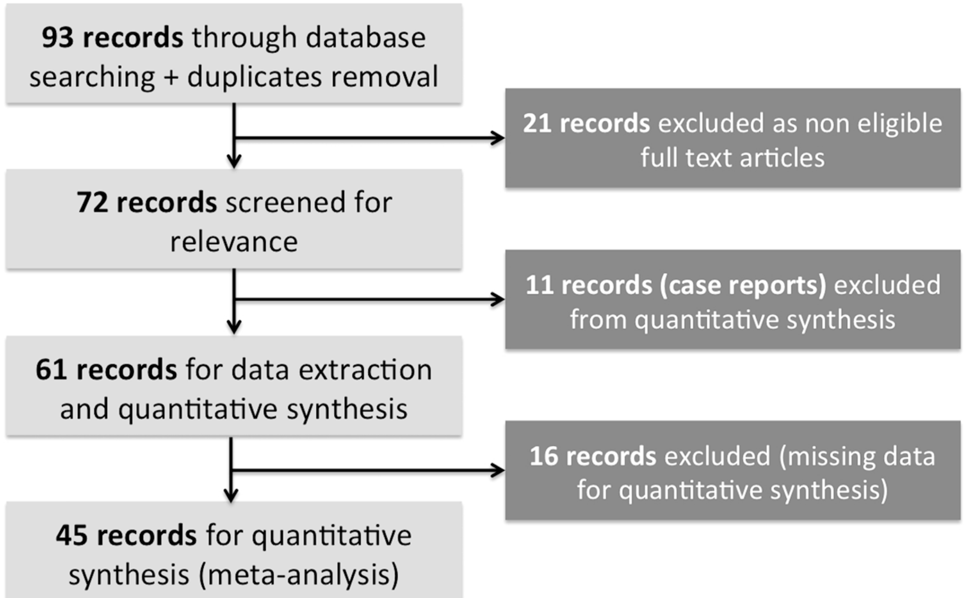

Fig. 1. Information flow through different phases of meta-analysis according to PRISMA guidelines.

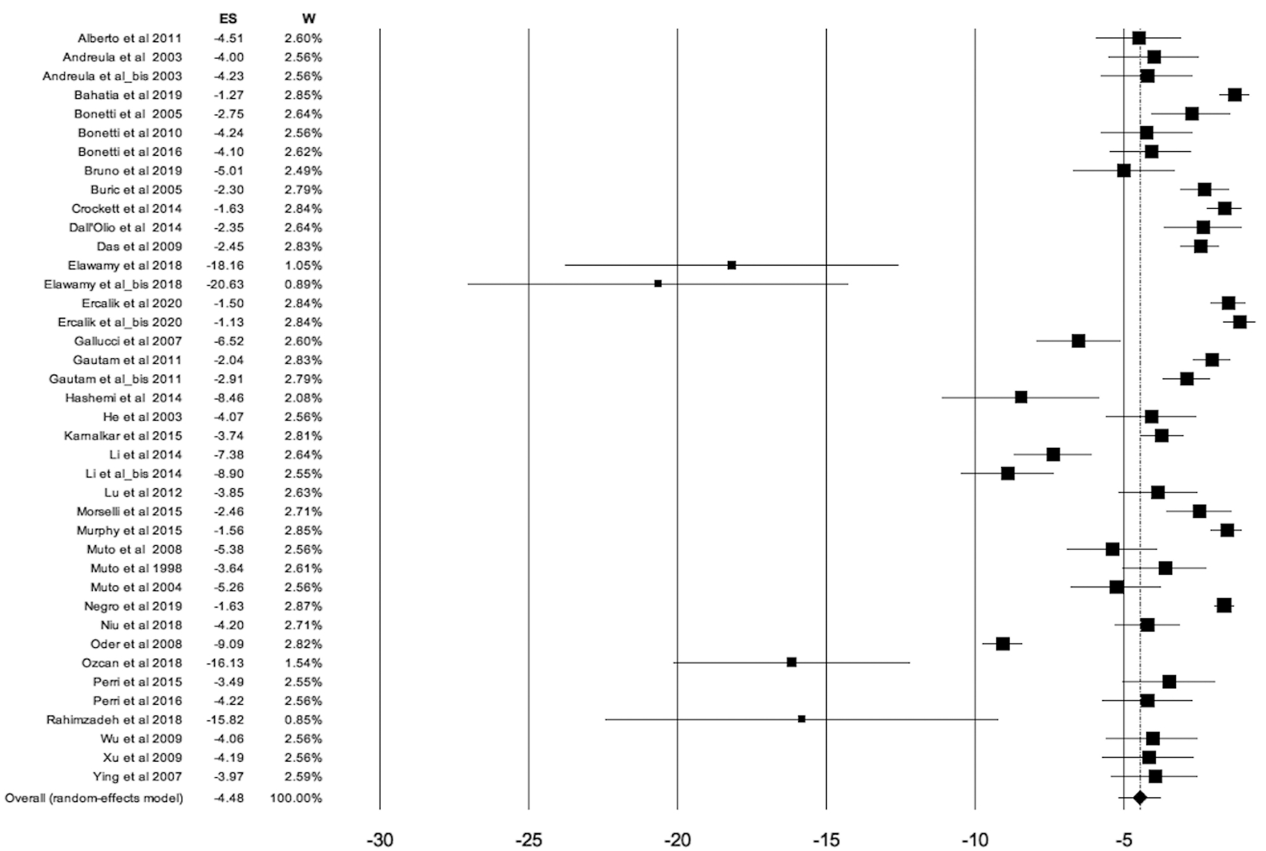

Fig. 2. Meta-analysis results with effect sizes (ES) and weightings (W) of each individual study included in the quantitative synthesis, and their overall effect size for image-guided oxygen-ozone injections.

significant degree of heterogeneity (92% and 95% respectively). Finally, as the random effect model is more sensitive to publication biases due to the relative weight given also to smaller studies, a funnel plot was also performed; publication biases analysis (obtained by examining the asymmetry in funnel plots) revealed a possible bias for image-guided oxygen ozone-therapy ($p < 0.0001$ at Egger's linear regression test), and to a lesser extent for non-image-guided procedures ($p < 0.037$). However, being the fail-safe number above the Rosenthal's rule of thumb in both cases, the likelihood of this publication bias is considered minimal hence negligible (Fig. 5).

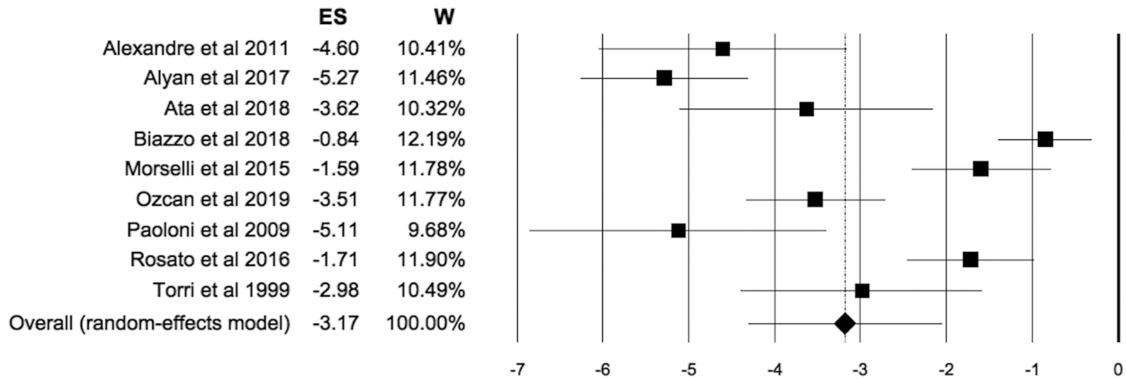

Fig. 3. Meta-analysis results with effect sizes (ES) and weightings (W) of each individual study included in the quantitative synthesis, and their overall effect size for non-image-guided oxygen-ozone injections.

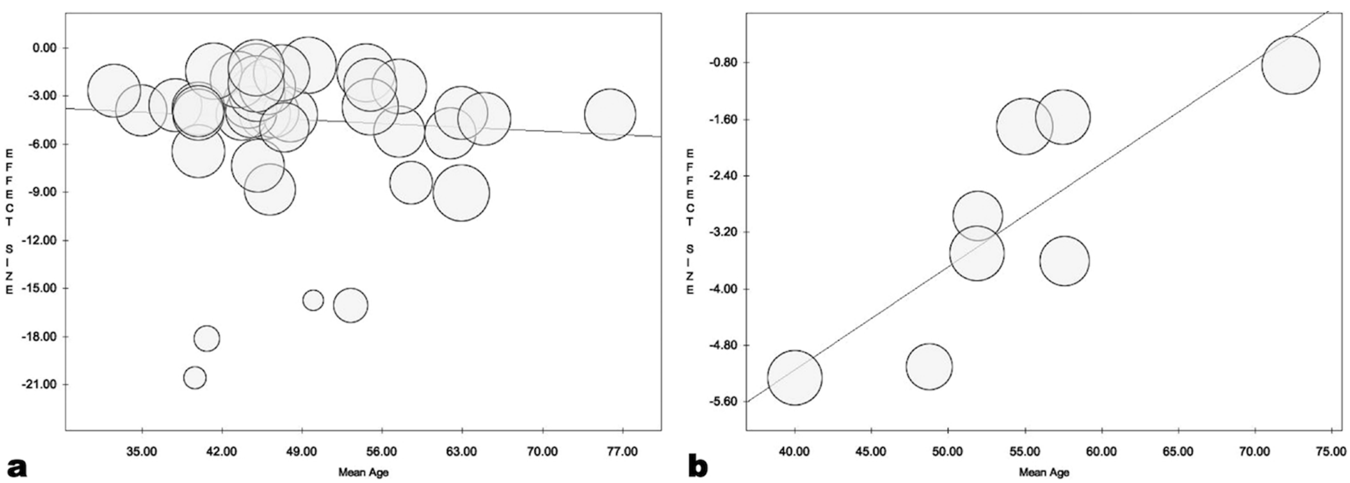

Fig. 4. Moderation graph for mean age, as moderator of effect size both in image-guided (*a*) and non-image-guided (*b*) oxygen-ozone injections.

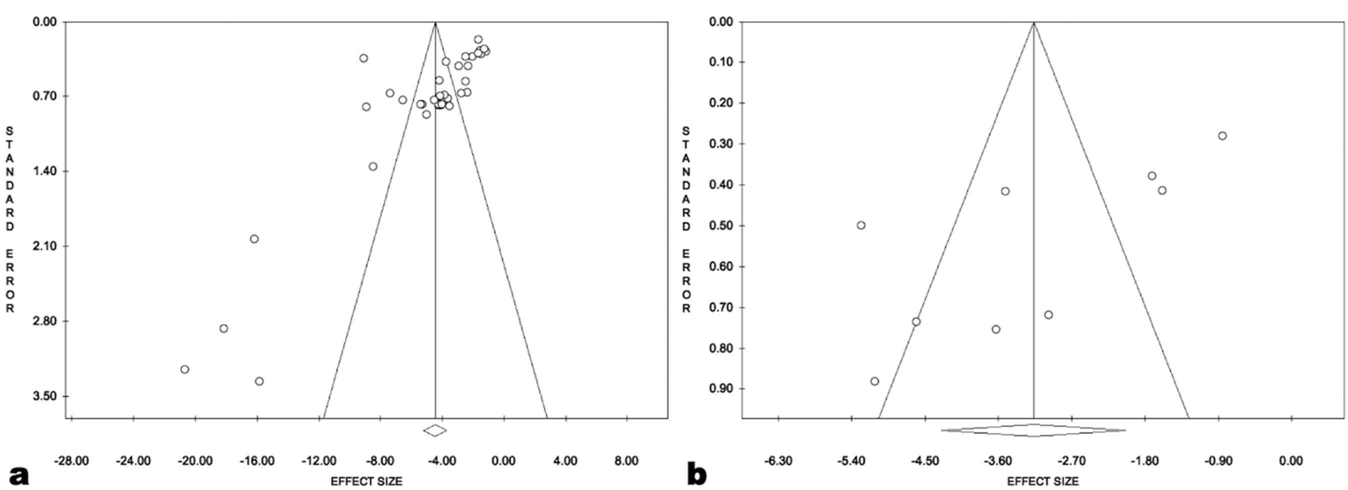

Fig. 5. Verification of publication bias graphically represented as a funnel plot displaying effect size and standard error both in image-guided (*a*) and non-image-guided (*b*) oxygen-ozone injections.

4. Discussion

Medical ozone is an analgesic, antiseptic, anti-inflammatory, immune-modulating gas, actinve on pro-inflammatory cytokines, prostaglandins and bradykinins synthesis [6–8]. Combined with low-concentrated oxygen, ozone is used for intramuscular/paravertebral and/or intradiscal injections; main indication is represented by LBP with or without radicular pain in absence of motor deficits, refractory to 4–6 weeks conservative therapy. In case of intradiscal administration, oxygen-ozone gaseous mixture can reduce intervertebral disc volume by oxidation of core proteins, resulting in disc contraction and volume reduction [9,10]. In case of paravertebral/intramuscular injection, the mixture produces anti-inflammatory effect on/around facet joint and nerve root coupled to relaxation of spinal muscles [5,11,12]. Since percutaneous oxygen-ozone injection was indicated as a possible treatment option for LBP, an open debate was held among experts concerning the injection method of choice. On the one hand, despite non-image-guided paravertebral injection generally provides an adequate LBP relief, the intervertebral discs needle positioning can only be obtained by using image-guided methods. On the other hand, image-guided techniques must be performed in an appropriate environment, imply exposure to ionising radiation and frequently requires anaesthesiologic support [13–19]. However no specific guideline or indication regarding the gold standard approach was produced till now, and few evidences concerning the direct comparison between the two techniques were collected.

In this meta-analysis, image-guided injections resulted in more effective pain relief with higher reduction in pain scales compared to non-image-guided procedures. Indeed fluoroscopic and CT image-guided injections techniques allow for a more accurate and deeper needle positioning, easing pain trigger targeting and ensuring correct needle tip localization by real-time tracking during therapy. In addition it also allows for intra-discal oxygen-ozone chemodiscolysis, which cannot be performed based on non-image-guided techniques. In this latter, intra-discal administration of medical ozone is associated to herniated lumbar disc volume reduction, with better results in case of higher pre-treatment herniated disc volume; our results are in line with previous studies documenting morphologic changes of herniated disc at post-operative magnetic resonance imaging (MRI) or CT scan of patients with discogenic disease [20–22]. These data are further corroborated by a single meta-analysis on ozone therapy for LBP secondary to herniated disc, comparing paravertebral/peri-foraminal versus intra-discal ozone administration, producing a strong recommendation in long-term pain relief for both techniques [23]. Our results also confirm previous studies showing the superiority of percutaneous oxygen-ozone therapy compared to non-pharmacological approaches and percutaneous drugs administration other than oxygen-ozone in reducing pain perception at follow-up [24–29].

In our analysis, non-image guided injections clinical outcomes seems to be particularly affected by patients' age compared to image-guided ones, with poor pain reduction and worst performance in older patients. The possible modifying effect of age on ozone therapy efficacy has been observed in several studies [21,22,30–32], although no comparison between image-guided and non-image guided procedures was available. Our results are probably due to the less effective localization of needle tip in non-image-guided injection techniques, coupled to the under-recognition of anatomical variants and osteoarthritis-related spinal modifications that could affect gaseous mixture release; these findings suggest that the variability due to patients' characteristics can be at least in part overcome by resorting to image-guided procedures, which ensure higher accuracy in localizing the optimal target for oxygen-ozone delivery.

Conversely, no difference between the two injections techniques emerged when testing moderators such publication year and journal IF. Regarding publication year, it should be noticed that in the early 2000 s there were more original articles on non-image-guided oxygen-ozone injections for LBP [33–39], whereas more recently a raising number of studies concerning image-guided oxygen-ozone injections was produced [40–42]; it can be assumed that, due to technical progression coupled to an ever-increasing number of clinical evidences on efficacy/safety of image-guided procedures, image-guided oxygen-ozone injections have been gradually taken over non-image-guided ones [42]. When incorporating in the analysis information regarding the two-years IF of the publishing journal, no difference emerged between the two groups; this evidence thus suggested no significant variability in scientific reliability of selected papers, as similar criteria have been homogeneously applied to all the research articles and rigorous revision processes have been granted by all the considered publishing journals. However it should be taken into account that the larger number of evidences were collected on image-guided rather than non-image-guided techniques, with a significant between-groups difference in terms of articles' sample sizes; moreover the higher the IF of the journal publishing a study is, the larger is the number of collected evidences used for research purposes, therefore increasing the weight and the relevance of the specific research to the scientific community.

Finally percutaneous oxygen-ozone therapy is usually described as a low risk procedure, also proposed for patients with former contraindications to neurosurgery. However, only few studies actually reported complications resulting from this therapy [43]. Severe complications secondary to oxygen-ozone therapy for LBP are sporadically documented and described in few case report/series. Severe complications are mainly represented by infections, vitreo-retinal haemorrhages, pneumocephalus, spinal cord or nerve injury; only two cases of fatal complications have been described, the first due to fulminating septicaemia secondary to infection at injection site and the second due to vertebro-basilar stroke. It should be noticed that these complications are related to patients' predisposing conditions (i.e. diabetes, immunodeficiency, etc), or more rarely to procedural errors (i.e. inadvertent intra-dural puncture, paradoxical embolism, etc). Minor complications are probably much more common but underreported; among these transitory and trivial side effects, the most frequent are represented by tachycardia, dizziness, itching, cutaneous reactions and hematoma at the infiltration point [43].

Possible limitations to the study include: single publicly available medical database used for bibliographic search and quantitative synthesis; possible biases deriving from between-groups heterogeneity according to $I2$ statistics; missing information concerning possible confounders (such as sex, body mass index, predisposing diseases, anatomical variants, etc.), as frequently unavailable at critical article analysis; arbitrary exclusion of non-Anglophone journals; absence of critical information concerning results stability over time after 6 months from the procedure (therefore long-term longitudinal follow-up has not be considered in the analysis).

In conclusion, percutaneous oxygen-ozone injection is a minimally invasive, cost-effective, repeatable and highly available procedure for the treatment of lumbar disc herniation-related low back pain when poorly responsive to conservative treatments. Although no consensus was reached on the superiority of image-guided oxygen-ozone injections compared to non-imaging-guided ones [44,45], in this first meta-analysis imaging-guided procedures showed a better therapeutic performance with higher impact on pain reduction and lower age-related variability. Concerning the heterogeneity in analysed literature results, our data also argue in favour of the need for a higher methodological rigor in patients' selection and stratification when oxygen-ozone therapy for LBP treatment is envisaged. Further studies are still required to assess the superiority of this method compared to conventional surgery and different mini-invasive techniques both in terms of efficacy and results' stability over time.

Ethical approval

NA.

Informed consent

NA.

Authors contribution

All authors make substantial contributions to conception and design, and/or acquisition of data, and/or analysis and interpretation of data according to ICMJE recommendations. All those who have made substantive contributions to the article have been named as authors.

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Conflict of Interest

The Authors declare that there is no conflict of interests.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejro.2021.100389.

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