INPLASY

Is medical ozone beneficial, effective and safe when used in patients treated with radiotherapy? Protocol for a scoping review for ongoing research

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Corresponding author:
Carla Garcia-Lourve Martin

carla.garca1@gmail.com

Author Affiliation:
Alicante University/ Research Unit Hospital Universitario Dr Negrín/ Fundación Instituto de Investigación Sanitaria Canarias.

Lourve, C[1]; Pérez-Cañaveras, MR[2]; Clavo-Varas, B[3]; Cánovas-Molina, A[4]; Castellano-Pérez, A[5]; Roncancio-Medina, T[6]; González-Beltrán, D[7]; de Juan Pérez, AI[8].

ADMINISTRATIVE INFORMATION

Support - CIGC2021 from Cabildo of LPGC.

Review Stage at time of this submission - Piloting of the study selection process.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202380090

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 20 August 2023 and was last updated on 20 August 2023.

INTRODUCTION

Review question / Objective Review question: Is medical ozone beneficial, effective and safe when used in patients treated with radiotherapy? Objective: The overall aim of this study is to describe the published evidence on the different interventions performed with medical ozone in patients treated with radiotherapy, specifically, to analyse the health outcomes of these interventions, to analyse the effectiveness according to the different methods for the different effects of radiotherapy and to review the aspects that directly influence patient safety.

Background Ozone (O3) is a triatomic molecule of oxygen. Is highly reactive and unstable gas, being the third most oxidizing molecule. When blood is ozonized, O3 reacts with cell membrane components, specifically the polyunsaturated fatty acids (PUFAs) of phospholipids, antioxidants, and plasma lipoprotein complexes; and when administered by RI, it reacts with glycocalyx, PUFAs and mucoproteins. This reaction leads to maximum oxidation of these components, producing four reactive oxygen species (ROS): ozonides, aldehydes, peroxides, and hydrogen peroxides (H2O2). ROS are normally released at low rates in healthy cells by a variety of metabolic pathways but when ROS production exceeds the cell's capacity to detoxify, oxidative stress occurs damaging cells, leading to deterioration of physiological function and cell death. This would sound as ozone is not a good therapeutic option but to maintain balance, cells have antioxidant

defenses regulated by pathways such as Nrf2/ARE and NFkb that are activated by O3.
Enzymatic activation mediated by second messengers produce several effects inducing an adaptive response of the organism in a hormesis dose-response relationship.
These include the regulation of oxidative stress, broad-spectrum germicidal activity against bacteria, fungi and viruses, and immunological modulation. Ozone also affects oxygen metabolism by changing blood rheological properties and increasing the rate of glycolysis. Clinically, this could translate into increased tissue perfusion. (Re, 2022; Clavo & Borrelli, 2023; Clavo et al., 2019; Jaffe, 1967; Schwartz & Sánchez, 2012; Adibhatla & Hatcher, 2010; Elvis & Ekta, 2011).

Rationale adiotherapy is a common treatment for cancer that works by producing oxidative stress in tissues, which can kill tumor cells but also damage healthy tissues. Ozone therapy has the potential to reduce oxidative stress, inflammation, and tissue damage, and has been studied in experimental models of various diseases. Radiotherapy is used in a large percentage of cancer patients as a main or adjuvant treatment. Its ionizing effect on irradiated tissues produces oxidative stress, which is a key mechanism for tumor cell death as well as for radiation-induced damage in healthy tissues. The potential of ozone therapy to modulate oxidative stress, inflammation, and tissue damage has been described in experimental models of several diseases. Radiotherapy is used in a large percentage of cancer patients as a main or adjuvant treatment. Its ionizing effect on irradiated tissues produces oxidative stress, which is a key mechanism for tumor cell death as well as for radiation-induced damage in healthy tissues. The potential of ozone therapy to modulate oxidative stress, inflammation, and tissue damage has been described in experimental models of several diseases.
In addition, there are no scoping reviews of reviews on the topic, which may clarify doubts and lead to investigations into gaps in the rationale for clinical practice.

METHODS

Strategy of data synthesis The search equation was structured using the PICOT question, eliminating the comparison component given the nature of the study: Adults undergoing radiotherapy treatment for cancer (patient), ozone therapy (intervention), ulcer size, ulcer grade, healing time, tissue toxicity, oxidative stress and inflammatory biomarkers (outcome), systematic reviews (type of study). Other health outcomes were taken into consideration. Terms and strings were defined with the assistance of an ozone therapist, radiation oncologist and specialized librarians from the HUDNGC.
Electronic Databases:
Six databases related to the biomedical sciences where selected: MEDLINE®, WOS-CC, SciELO Citation Index, KCI-Korean Journal Database, EMBASE, CINAHL
This will be performed following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins, J et al (2008)) using information retrieval systems (IR systems) such as WOS (MEDLINE®, WOS-CC, SciELO Citation Index, KCI-Korean Journal Database) CISNE and EMBASE.
WOS:
(TS=(Radiotherapy) OR TS=(Radiation Oncology) OR AB=(radia*) OR AB=(radio*)) AND (TI=(ozon*) OR TS=(ozone)) AND ((TS=(Wound Healing) OR TS=(Wounds and Injuries) OR TS=(Re-Epithelialization) OR TS=(Ulcer) OR TS=(Skin Ulcer) OR TS=(tissue damage) OR TS=(tissue*) OR TS=(wound)) OR (TS=(health) OR TS=(effect*) OR TS=(outcome) OR TS=(Oxidative Stress) OR TS=(toxic*) OR TS=(adverse*) OR TS=(Reactive Oxygen Species) OR TS=(complication*)) OR (TS=(patient safety) OR TS=(safe*))) AND (Review Article (Document Types)) AND (Web of Science Core Collection OR MEDLINE® OR KCI-Korean Journal Database OR SciELO Citation Index (Database)).

Eligibility criteria Research papers had to meet the following inclusion criteria:
The studies must cover health topics.
Reviews of all kinds
Ozone therapy exposure, regardless of dose, concentration, duration or route of administration (systemic (rectal, autohemotherapy) or local (topical).
On the other hand, articles meeting any of the following criteria were excluded:
Ozone therapy is not used to prevent or treat radiation-induced effects and complications.
Non-treatment with radiotherapy
In vitro studies and animal models.
Scientific opinion articles, protocols, brief reports, perspectives, research letters, letters to the editor, conference abstracts.
Studies in which it is not possible to obtain the full text
Research papers had to meet the following inclusion criteria:
The studies must cover health topics.
Systematic reviews
Ozone therapy exposure, regardless of dose, concentration, duration or route of administration

(systemic (rectal, autohaemotherapy) or local (topical).
On the other hand, articles meeting any of the following criteria were excluded:
Ozone therapy is not used to prevent or treat radiation-induced effects and complications.
Non-treatment with radiotherapy
In vitro studies and animal models.
Scientific opinion articles, protocols, brief reports, perspectives, research letters, letters to the editor, conference abstracts, systematic narrative.
Studies in which it is not possible to obtain the full text.

Source of evidence screening and selection Four reviewers will screen by title and abstract the reports retrieved by de information retrieval systems (IR systems) such as WOS, EBSCOHost and EMBASE. In case of discrepancies, we will be inclusive. Subsequently, when all the sources have been reviewed by at least 2 reviewers, we will run a second screen by reading the full text. The selected reports will be screened by 2 reviewers. Disagreements at this stage will be discused with experts in the field (Biologist, Radiation Oncologist, Ozone therapist, methodologists, ect.) The reasons for the exclusion will be indicated.
The screening process will be carried out in Rayyan sofware (https://rayyan.ai/reviews/708634).

Data management Data will be extracted individually by using a form specifically designed for this review (Google Form) and the data will be displayed in a table format were the information will be contained: study identification (Authors, year, journal) type of review, language, number of studies included, type of intenventions, financial support, outcomes and quality.

Reporting results / Analysis of the evidence As we expect a heterogeneous sample, we will perfom a narrative synthesis. If we retrieve a sample that shows homogeneity among several studies, a meta-analysis will be performed.

Presentation of the results Results will be presented in a tables and figures for better understanding of the process and results.

Language restriction No.

Country(ies) involved Spain.

Other relevant information This protocol is a preliminary search to retrieve information for future and ongoing reviews on the subject by our research group.

Keywords ozone; ozone therapy; Radiotherapy; Radiation Oncology; Patient Safety.

Dissemination plans if the findings are worthwhile, we will disseminate the results by trying to publish our results in the adequate indexed journal. If the paper is not accepted, we will propose it to a second journal and so on in a cascading order of subject suitability.

Contributions of each author
Author 1 - Carla Garcia-Lourve Martin - Drafted the manuscript and created the protocol. Was a reviewer, developed the selection criteria, and the risk of bias assessment strategy. Screened and reviewed the dataset and extracted the data. Will write the final report.
Email: carla.garca1@gmail.com
Author 2 - Rosa María Pérez-Cañaveras - Contributed to the development of the methodology (search strategy, selecction of tools, selection criteria, and the risk of bias assessment). Will review the final manuscript.
Author 3 - Bernardino Clavo-Varas - Advised on theory, recommended key words and terms, and reviewed the protocol and will review the final manuscript.
Author 4 - Ángeles Cánovas-Molina - Was a reviewer, contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 5 - Antonia Castellano-Pérez - Was a reviewer, contributed to the development of the selection criteria, and the risk of bias assessment strategy.
Author 6 - Tatiana Roncancio-Medina - Will review the protocol and final manuscript.
Author 7 - Damián González-Beltrán - Was a reviewer.
Author 8 - Alba Isabel de Juan Pérez - Will review the final manuscript.