

**Oxygen-ozone therapy in human clinical practice: an integrative literature review***Terapia de oxígeno-ozono en la práctica clínica humana: una revisión integrativa de la literatura**Oxigênio-ozonioterapia na prática clínica humana: uma revisão integrativa de literatura***Abstract**

The aim was to summarize the recent scientific evidence related to the practice of oxygen-ozone therapy in human clinical care. Integrative review with the inclusion of articles in Portuguese, English and Spanish, published between 2018 and 2021. Databases used: VHL; CINAHL; BASE; COCHRANE; PUBMED; and, WoS. The descriptors were chosen using the acronym PICO of the guiding question. For the development of the review, the recommendations of the Guideline Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) were followed and the level of evidence of the articles was evaluated according to the Oxford Centre. Included 24 articles whose research methods were: Case Reports (33.3%); Clinical Trials (33.3%); Systematic Reviews (12.5%); Scoping Review (4.2%); Case-control study (8%); Quasi-experimental study (4%); and, Case Series (4%). The main conditions treated with oxygen-ozone therapy were: osteoarticular diseases; COVID-19; infections; wounds; fibromyalgia. Yet, the process of assisted reproduction. The degree of recommendation of the analyzed studies, according to Oxford, were: 54.2%, Grade A; 12.5%, Grade B; and 33.3% Grade C. As an innovative integrative and complementary therapeutic approach, Oxygen-Ozone Therapy was identified as successfully applicable for the treatment of specific health situations in different scenarios.

**Descriptors:** Ozone; Evidence-Based Nursing; Medicine; Evidence-Based Clinical Practice; Integrative and Complementary Health Practices.

**Resumén**

El objetivo fue resumir la evidencia científica reciente relacionada con la práctica de la oxigenoterapia con ozono en la atención clínica humana. Revisión integradora con inclusión de artículos en portugués, inglés y español, publicados entre 2018 y 2021. Bases de datos utilizadas: BVS; CINAHL; BASE; COCHRANE; PUBLICADO; y WoS. Los descriptores fueron elegidos utilizando la sigla PICO de la pregunta orientadora. Para el desarrollo de la revisión se siguieron las recomendaciones de la Guideline Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) y se evaluó el nivel de evidencia de los artículos según el Oxford Centre. Se incluyeron 24 artículos cuyos métodos de investigación fueron: Informes de Casos (33,3%); Ensayos Clínicos (33,3%); Revisiones Sistemáticas (12,5%); Revisión de Alcance (4,2%); Estudio de casos y controles (8%); Estudio cuasi-experimental (4%); y Serie de Casos (4%). Las principales patologías tratadas con oxígeno-ozonoterapia fueron: enfermedades osteoarticulares; COVID-19; infecciones; heridas; fibromialgia Y sin embargo, el proceso de reproducción asistida. El grado de recomendación de los estudios analizados, según Oxford, fue: 54,2%, Grado A; 12,5%, Grado B; y 33,3% Grado C. Como enfoque terapéutico integrador y complementario innovador, la Terapia de Oxígeno-Ozono fue identificada como aplicable con éxito para el tratamiento de situaciones específicas de salud en diferentes escenarios.

**Descriptoros:** Ozono; Enfermería Basada en la Evidencia; Medicamento; Práctica Clínica Basada en Evidencia; Prácticas de Salud Integrativas y Complementarias.

**Resumo**

Objetivou-se sumarizar as recentes evidências científicas relacionadas à prática da terapia oxigênio-ozônio no atendimento clínico humano. Revisão integrativa com inclusão de artigos nos idiomas português, inglês e espanhol, publicados entre 2018 e 2021. Bases de dados utilizadas: BVS; CINAHL; EMBASE; COCHRANE; PUBMED; e, WoS. Os descritores foram escolhidos mediante o acrônimo PICO da questão norteadora. Para o desenvolvimento da revisão seguiram-se as recomendações do Guideline Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) e, foi realizada avaliação do nível de evidência dos artigos segundo Oxford Centre. Incluídos 24 artigos cujos métodos de pesquisa foram: Relatos de Casos (33,3%); Ensaios Clínicos (33,3%); Revisões Sistemáticas (12,5%); Scoping Review (4,2%); Estudo Caso-controle (8%); Estudo Quase-experimental (4%); e, Série de Casos (4%). Os principais acometimentos tratados com oxigênio-ozonioterapia foram: as doenças osteoarticulares; COVID-19; infecções; feridas; fibromialgia. E ainda, o processo da reprodução assistida. O grau de recomendação dos estudos analisados, conforme Oxford, foram: 54,2%, Grau A; 12,5%, Grau B; e, 33,3% Grau C. Como uma inovadora abordagem terapêutica integrativa e complementar, a Oxigênio-Ozonioterapia foi apontada como aplicável com sucesso para o tratamento de situações de saúde específicas em diversos cenários.

**Descriptoros:** Ozônio; Enfermagem Baseada em Evidências; Medicina; Prática Clínica Baseada em Evidências; Práticas de Saúde Integrativas e Complementares.

**Karyta Jordana Santos de Paula<sup>1</sup>**

ORCID: 0000-0002-3968-8098

**Marcia Helena de Souza Freire<sup>1</sup>**

ORCID: 0000-0003-3941-3673

<sup>1</sup>Universidade Federal do Paraná.  
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**Corresponding author:**

Karyta Jordana Santos de Paula  
E-mail: [karytajordana@gmail.com](mailto:karytajordana@gmail.com)

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## Introduction

In nature, Ozone (O<sub>3</sub>) is a triatomic molecule of Oxygen, which is in the gaseous state, colorless, with a characteristic odor, produced by electric discharge incident on molecules of Oxygen (O<sub>2</sub>), constituting the Ozone Layer of the troposphere. This protects us from excessive ultraviolet radiation, which is why it is also known as the Gas of Life<sup>1</sup>. However, its production can also be carried out by medical equipment, the medical ozone generator, through a high voltage electrical discharge, which promotes the breakage of the O<sub>2</sub> molecule and, subsequently, the reorganization of the molecules generating a compound gas mixture by O<sub>2</sub> and O<sub>3</sub>. This mixture has been used for over a century, initially mainly to treat war wounds. It is therapeutically applied in precise concentrations, starting from medicinal oxygen with a purity of up to 99.9%, within a range or therapeutic scale, and was called Ozone Therapy<sup>2</sup>, also known as, Oxygen-Ozone Therapy (O<sub>2</sub>/O<sub>3</sub>), or Oxygen-Ozone Therapy.

As a highly reactive gaseous molecule, O<sub>3</sub> rapidly dissolves in water, plasma and extracellular fluids. However, the close dependence on temperature and pH of the medium makes it unstable. Reacting O<sub>3</sub>, when in contact with biomolecules, generates its by-products, generically called ozonides, namely: Hydrogen Peroxide (H<sub>2</sub>O<sub>2</sub>); Superoxide (O<sub>2</sub>•); Hydroxyl Radical (OH•); and, Nitric Oxide (NO•)<sup>1,3</sup>. From which it can be concluded that the characteristics of the microenvironment in which the O<sub>3</sub> reaction will occur, from a clinical point of view, will influence the relevance of the oxidizing action of the gas<sup>3</sup>.

In general, as for its clinical effects, they result from the reaction of O<sub>3</sub> that reacts with the molecules of lipids, proteins, carbohydrates and nucleic acids, promoting, through mediating molecules: better transport of oxygen to the tissues; activation of the immune system; release of growth factors; release of so-called gifted erythrocytes; release of stem cells; and, the regulation of antioxidant enzymes<sup>3</sup>. It is also understood that O<sub>3</sub> does not follow the fundamental principles of classical pharmacology such as absorption, distribution, metabolism and excretion, and the mechanism of action of systemic therapy with O<sub>3</sub> is an indirect effect. It acts as a modulator or prodrug and by inducing secondary messengers, it enhances subsequent adaptive responses. After this quick reaction, which happens in seconds, the O<sub>3</sub> disappears<sup>4</sup>.

Based on its properties, O<sub>3</sub> is capable of promoting rapid, subtle and transient oxidative stress, which, in turn, restores signaling pathways lost in pathological conditions, preserving cellular redox balance. It increases endogenous antioxidant action through mitochondrial function, as well as regulates transcription factors, in addition to having an immunomodulatory effect due to the positive and negative feedback of inflammatory cytokines (ex: Interleukins) and pro-inflammatory (ex: Interferon- $\alpha$  [TNF- $\alpha$ ]). Thus, Ozone Therapy induces the simultaneous rescue of decompensated physiological activities, reactivating and rebalancing them<sup>5</sup>.

It is emphasized that, precisely because it rebalances decompensated physiological reactions, Ozone Therapy is considered complementary and adjuvant to the

standard treatment of various health problems, favoring the effectiveness of drugs and other conventional therapies implemented.

In the Brazilian scenario, Ozonotherapy was included and recognized, in March 2018, as a new practice included in the National Policy on Integrative and Complementary Practices (PNPIC) of the Unified Health System (SUS). Being pointed out the proven scientific efficacy of its therapeutic potential, especially regarding the bactericidal, fungicidal, inactivation of yeasts and parasites actions, in addition to having an immunomodulatory effect and, potentiating tissue regeneration<sup>6</sup>.

Thus, the growing scientific evidence produced has pointed to its safe therapeutic effects, in addition to highlighting the measures to prevent the limited undesirable effects, more related to the contraindications of the application of therapeutic ozone in human health care<sup>7-9</sup>. Thus, in order to contribute to the consolidation of the knowledge of professionals and managers in the health area, as well as users about O<sub>2</sub>/O<sub>3</sub> Therapy, there is a need to continue research so that the evidence can be identified, synthesized and disseminated.

The objective was to summarize the recent scientific evidence published on Oxygen-Ozone Therapy applied in human clinical practice.

## Methodology

This is an integrative review with a time frame for the scientific publications of the last 3 years. Based on the methodological framework of Whittemore and Knaf<sup>10</sup>, carrying out the following steps: 1) Identification of the problem; 2) Search in the literature; 3) Data evaluation; 4) Data analysis; 5) Presentation of results. This review followed, from its conception to formatting for publication, the recommendations of the Guideline Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement<sup>11</sup>.

Thus, the guiding question was constructed with the help of the PICO strategy (Patient/Problem, Intervention, Context), which is essential for the construction of questions that seek evidence for clinical practice<sup>12</sup>.

The research question was defined as: What is the recent scientific evidence of the use of Oxygen-Ozone Therapy in human clinical practice? In which the Population referred to people receiving the therapy under study, the adult segment was adopted (no age range specified); Intervention, Medicinal Ozone or Ozone Therapy or Oxygen-Ozone Therapy or Oxygen-Ozone Therapy itself; o Co, as a context for the application of Ozone Therapy in clinical situations conveyed by articles in the area of traditional complementary medicine or integrative health.

From the research question, more specifically the PICO elements, and the objective, the descriptors (DeCs – Health Sciences Descriptors, and MeSH – Medical Subject Headings) presented in Chart 1 were determined. These, combined with the Boolean operators “OR” and “AND”, allowed us to trace search strategies in the databases, as shown in Chart 2.



Data were collected on February 18, 2021. Searches were performed in the databases of the Virtual Health Library (BVS), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Embase Indexing and Emtree®

(EMBASE), Cochrane Library (COCHRANE), National Library of Medicine (PUBMED) and Web of Science (WoS), whose strategies are presented in Chart 2.

**Chart 1.** Descriptors related to the elements of the PICo strategy and applied in the literature review. Curitiba, PR, Brazil, 2021

Elements	Descritores	Descriptors	Descritores
P	Adulto	Adult	Adulto
I	Ozônio	Ozone Therapy	Terapia Ozono
Co	Medicina	Medicine	Medicina

Note: P – Population; I – Intervention; Co - Context.

**Chart 2.** Search strategies using descriptors, entry terms and boolean operators in databases. Curitiba, PR, Brazil, 2021

BVS	((“Ozone Therapy” OR “Terapia Ozono”) AND (“Medicine” OR “Medicina”) AND (“Adult” OR “Adulto”))
CINAHL, COCHRANE, WoS	((“Ozone Therapy”) AND (“Medicine”))
EMBASE	‘ozone therapy’ AND (‘analgesic agent’/dd OR ‘antifungal agent’/dd OR ‘antiinfective agent’/dd OR ‘antineoplastic agent’/dd OR ‘antioxidant’/dd OR ‘corticosteroid’/dd OR ‘local anesthetic agent’/dd OR ‘nonsteroid antiinflammatory agent’/dd OR ‘oxidizing agent’/dd OR ‘ozone’/dd) AND (‘chronic disease’/dm OR ‘diseases’/dm OR ‘inflammation’/dm OR ‘pain’/dm) AND (‘clinical trial’/lnk OR ‘therapy’/lnk) AND [18-2-2018]/sd NOT [19-2-2021]/sd
PUBMED	((“Ozone Therapy”) AND (“Medicine”) AND (“Adult”))

Note: VHL – Virtual Health Library; CINAHL - Cumulative Index to Nursing and Allied Health Literature; COCHRANE - Cochrane Library; EMBASE - Embase Indexing and Emtree; PUBMED - National Library of Medicine; WoS - Web of Science.

The inclusion criteria were articles in the form of Systematic Reviews, Clinical Studies, Cohort, Ecological, Case-Control, Case Series and Case Reports; complete and available in full; in Portuguese, English and Spanish; who answered the research question; and, published between January 1, 2018 and February 18, 2021. The period of the last three years is justified due to the search for more current publications.

Theoretical articles, integrative and narrative reviews (because they presented low evidence compared to Systematic Reviews), editorials, theses, dissertations, monographs, abstracts, documents, event proceedings and guidelines, in addition to those related to veterinary medicine and dentistry, were excluded. Studies with duplicate titles were counted only once.

Regarding the COCHRANE database, in which 11 results of clinical studies were retrieved, some of them were from years before the time limit of the research, inserted in the base only from 2018; others were not available for reading in full. Therefore, no articles from this database were included in this study.

Finally, 178 articles were identified, and after removing the duplications with the aid of the Mendeley® reference manager software, 149 studies remained. After reading titles and abstracts, another 110 articles were excluded due to non-availability in full (n=22); not answering the research question (n=70); articles related to veterinary medicine (n= 07); non-scientific articles such as articles from non-scientific journals and folders (n=05); and, narrative and integrative reviews (n=06).

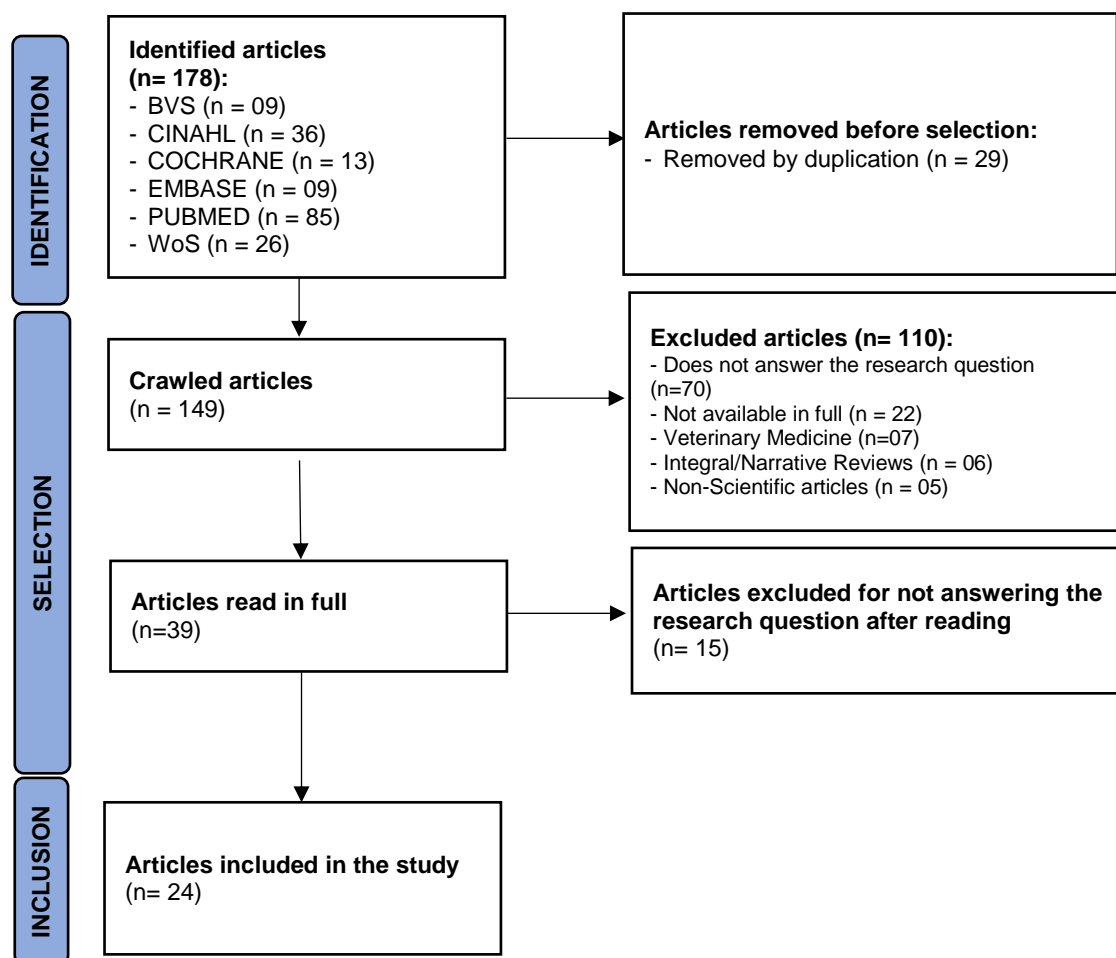
After careful reading of the 39 remaining manuscripts, in full, another 15 of them were excluded for

not answering the research question. The sample of this review totaled 24 articles, which presented results responsive to the proposed research question, as shown in the adapted Flowchart PRISMA<sup>11</sup> (Figure 1).

The selected studies were submitted to the evidence classification of the Oxford Center for Evidence-based Medicine Levels of Evidence Grades of Recommendation<sup>13</sup>. The levels of evidence are used as guides in the classification process of the quality of scientific studies and are ranked according to the design of the primary studies. Knowing these levels, it is possible to classify the information obtained in the reading of the articles in degrees of recommendation (which have classification A, B, C and D) and level of evidence (which are subclassifications)<sup>14</sup>. The correspondence between the degree of recommendation and the strength of scientific evidence established by the Oxford Center aims to give transparency to the origin of the information, stimulate the search for stronger scientific evidence, helping the reader to criticize.

For discussion and analysis, the 24 articles included in the present review were organized in a table and some variables were highlighted, namely: article order number; year of publication (sorted in ascending sequence); authors' names, as listed in the bibliographic reference; year of publication (2018, 2019, 2020 and 2021), noting that for the year 2021, publications occurred until February 18, due to the schedule of data collection; country of publication; method adopted for the development of the study; degree of recommendation and/or evidence (REC/EVI) of the generated results; the main results and limitations of each analyzed study

Figure 1. Flowchart of search and selection of articles. Curitiba, PR, Brazil, 2021



Source: As per PRISMA recommendation<sup>11</sup>.

## Results and Discussion

The scientific articles identified were published in 2018 (6; 25%), 2019 (6; 25%), 2020 (9; 38%) and in the first two months of 2021 (3; 12%). It is noteworthy that studies published in several regions of the world were identified, with a predominance of Europe - Spain and Italy (8; 33.3%), followed by the Middle East - Iran and Turkey (6; 25.0%), by the Region of Americas – USA and Brazil (5; 20.8%), Asia – India and China (4; 16.7%) and Africa – Egypt (1; 4.2%) (Chart 3).

Germany was the birthplace of ozone therapy, starting in 1840, when a physicist, Christian Friedrich Schonbein discovered ozone by working with a voltaic cell in the presence of oxygen. In addition, he could verify that there was in the place a gas with a pungent odor, which he called ozone, from the Greek ozein, relative to what gives off odor, smell. Thus, Germany was the first country to industrialize ozone generators. Its first medical application, according to Velio Bocci<sup>15</sup>, an Italian physician and pioneer researcher of ozone, took place in World War I for the treatment of gaseous and post-traumatic gangrene in German soldiers. Later, a Swedish dentist was the first to use it in his practice. In 1936, a physician in France proposed rectal insufflation using a gas mixture of O<sub>2</sub>/O<sub>3</sub> to treat chronic colitis and fistula. Therefore, the medicinal application of ozone has slowly developed over the last

century, gaining countries and adepts all over the world, a scenario stimulated by its disinfecting properties<sup>15</sup>.

Authors<sup>16</sup> point to the development of Ozone Therapy in some countries according to the prevalent area. Germany has applied ozone therapy in vascular surgery, stomatology and geriatrics; Italy focused its activities on medical cosmetology; Switzerland and other Western European countries have specialized therapeutic clinics; the Ozone Research Centers are concentrated in Cuba and, are recognized worldwide, currently there are 39 Medical Centers for Ozone Therapy<sup>16</sup>; in the United States, Ozone Therapy is present in 13 states<sup>16</sup>; Japan has also shown interesting results with medical ozone. In Brazil, Ozone Therapy was introduced in 1975, by the German doctor living in our country, Dr Heinz Konrad<sup>15</sup>, and is still being organized and legalized by the Professional Councils, with significant advances in Dentistry and Veterinary Medicine.

Among the research methods, the following were identified: eight Case Reports (33.3%)<sup>18-25</sup>; eight Clinical Trials (33.3%)<sup>26-28</sup>, among these, a controlled<sup>29</sup>; two randomized<sup>30-31</sup>, and two double blind<sup>32-33</sup>; three Systematic Reviews (12.5%)<sup>34-36</sup>; one Scoping Review (4.2%)<sup>37</sup>; two case-control study (8.3%)<sup>38-39</sup>; a quasi-experimental study (4.2%)<sup>40</sup>; and, one Multiple Case Study (4.2%)<sup>41</sup> (Chart 3).

As for the objectives, researches with themes concerning: skin lesion by ectoparasite bite (n=1; 4.2%)<sup>19</sup>;



use of ozone as a complementary therapy in assisted reproduction (n=1; 4.2%)<sup>20</sup>; treatment of wounds resulting from complications of diabetes mellitus (n=2; 8.3%)<sup>21,24</sup>; complementary treatment of abscesses and septic infections (n=2; 8.3%)<sup>18,29</sup>; pain management in herniated discs (n=3; 12.5%)<sup>26-27,30</sup>; chronic pain management in knee osteoarthritis (n=4; 16.7%)<sup>34-36,40</sup>; use of ozone for analgesia, monotherapy, associated and/or compared to other anti-inflammatory agents (n=5; 20.8%)<sup>22,25,28,32-33</sup>; and, in the management of Coronavirus Disease – 2019, COVID-19 (n=6; 25%)<sup>23,31,37-39,41</sup> (Chart 3).

The studies analyzed showed 54.2% Degree of Recommendation "A", 12.5% Degree of Recommendation "B", and 33.3% Degree of Recommendation "C". Regarding the Level of Evidence (LE), it was observed in this review that most of the analyzed studies (n= 8; 33.3%) were publications of Case Reports, LE of 4, therefore presenting the lowest level of evidence. However, in the sequence, we present the Randomized Clinical Studies (n=5; 20.8%), categorized in NE = 1B, those that generate evidence of quality; and, in the continuity, the Systematic Reviews, 16.7% of the studies (n=4), are of LE = 1A, constituting as the top of the best evidences. Studies with therapeutic results or presented as a case series constitute the NE = 1C (n=4; 16.7%); studies with observation of therapeutic results reach NE = 2C (n=1; 4.2%); and, the Case-Control studies that cover the NE = 3B (n=2, 8.3%).

It is understood that conducting Randomized Clinical Trials is not an easy task, as it depends on a logistical organization and competent personnel for the development, in addition to a group of researchers who discuss the outcomes and emerging problem-situations. Added to this difficulty is the approach to Ozone Therapy, as it still constitutes a 'new' integrative and complementary therapeutic approach, with insufficient standardization and regulation for several countries, including Brazil.

One of the facts that weigh for the safe practices of Ozone Therapy by health professionals is the infringement of the patent principle, related to the pharmaceutical industries. It is understood that the mixture of oxygen-ozone as a physiological modulating agent, and ozone as a biological molecule, that is, produced in our metabolic process, does not have the support of the pharmaceutical industry for the impetus of quality multicentric studies.

However, in March 2018, Ozone Therapy was included and recognized as a new practice integrated into the National Policy on Integrative and Complementary Practices (PNPIC), with the justification of having proven scientific efficacy of therapeutic potential, which are due to bactericidal actions, fungicides, inactivation of yeasts and parasites, in addition to causing an immunomodulatory effect and potentiating tissue regeneration<sup>6</sup>.

**Chart 3.** Articles in summary by serial number, authors, year and country of publication, method applied, degree of recommendation and/or evidence, main results and study limitations, Curitiba, PR, Brazil, 2021

No.	AUTHORS	YEAR	COUNTRY	METHOD	REC/LE	TITLE	GENERAL OBJECTIVE OF THE STUDY	STUDY LIMITATION
1	Rowen <sup>18</sup>	2018	USA	Case report	C/4	Ozone therapy in conjunction with oral antibiotics as a successful primary and sole treatment for chronic septic prosthetic joint: review and case report	Report the case of use of ozone for chronic septic infection in prosthetic joint.	Low level of evidence
2	Rowen <sup>19</sup>	2018	USA	Case report	C/4	Ozone therapy as a primary and sole treatment for acute bacterial infection: case report	Report the case of acute bacterial infection due to tick bite cellulitis.	Low level of evidence
3	Merhi, Moseley-LaRue, Moseley, Smith, Zhang <sup>20</sup>	2019	USA	Case report	C/4	Ozone and pulsed electromagnetic field therapies improve endometrial lining thickness in frozen embryo transfer cycles. Three case reports	Report three cases of the use of ozone to improve endometrial lining thickness in frozen embryo transfer cycles.	Low level of evidence
4	Gao, Li, Wang, Wang <sup>21</sup>	2019	CHINA	Case report	C/4	Comprehensive treatment of diabetic hallux gangrene with lower extremity vascular disease: A case report	Describe a case of diabetic gangrene of the hallux with vascular disease of the lower extremity, which was treated by surgical debridement, ozone therapy and interventional vascular surgery.	Low level of evidence
5	Rowen, Robins <sup>22</sup>	2019	USA	Case report	C/4	Ozone Therapy for Complex Regional Pain Syndrome: Review and Case Report	Introduce ozone therapy as a novel approach to pain management, including Complex Regional Pain Syndrome.	Low level of evidence
6	Hernández, Viñals, Isidoro, Vilás <sup>23</sup>	2020	SPAIN	Case report	C/4	Potential Role of Oxygen-Ozone Therapy in Treatment of COVID-19 Pneumonia	Report the potential effect of oxygen-ozone therapy in the treatment of COVID-19 pneumonia.	Low level of evidence
7	Marchesini, Ribeiro <sup>24</sup>	2020	BRAZIL	Case report	C/4	Efeito da ozonioterapia na cicatrização de feridas	Verify the effect of ozone therapy on the healing of a chronic wound in a patient with diabetes mellitus.	Low level of evidence



8	Bellomo, Paolucci, Giannandrea, Pezzi, Saggini <sup>25</sup>	2020	ITALY	Case report	C/4	Ozone Therapy and Aquatic Rehabilitation Exercises to Overcome the Lumbar Pain Caused by Facet Joint Syndrome – Case Report	Evaluate the therapeutic results of percutaneous ozone injection for acute low back pain caused by Facet Joint Syndrome.	Low level of evidence
9	Ozcan, Muz, Yildiz Altun, Onal <sup>26</sup>	2018	TURKEY	Clinical Trial	A/1C	Intradiscal ozone therapy for lumbar disc herniation	Determine the effect of intradiscal injection of ozone on pain score and satisfaction of patients with low back pain.	Lack of control group
10	Ezeldin, Leonardi, Princiotta, Dall'olio, Tharwat, Zaki, et al. <sup>27</sup>	2018	EGYPT	Clinical Trial	A/1C	Percutaneous ozone nucleolysis for lumbar disc herniation	Prospectively evaluate the effectiveness of ozone in the treatment of contained or uncontained lumbar disc in herniated discs.	Lack of control group; small sampling; and, reduced follow-up time
11	Tirelli, Cirrito, Pavanello, Piasentin, Lleshi, Taibi <sup>28</sup>	2019	ITALY	Clinical Trial	A/1C	Ozone therapy in 65 patients with fibromyalgia: an effective therapy	Verify the effect of ozone therapy in patients with fibromyalgia.	Obscure method
12	Xu, Liu, Wang, Li, Yang, Du, et al. <sup>29</sup>	2018	CHINA	Controlled Clinical Trial	A/1B	Computed tomography-guided catheter drainage with ozone in management of pyogenic liver abscess	Compare the effectiveness of treatment of percutaneous catheter drainage alone with catheter drainage combined with ozone in the management of pyogenic liver abscess.	Unicentric
13	Niu, Lv, Yi, Tang, Gong, Niu <sup>30</sup>	2018	CHINA	Randomized Clinical Trial	A/1B	Therapeutic Effect of Medical Ozone on Lumbar Disc Herniation	Investigate the therapeutic effect of low, medium and high concentrations of ozone on trauma-induced lumbar disc herniation.	Short follow-up time (12 months)
14	Shah, Captain, Vaidya, Kulkarni, Valsangkar, Nair, et al. <sup>31</sup>	2021	INDIA	Randomized Clinical Trial	A/1B	Safety and efficacy of ozone therapy in mild to moderate COVID-19 patients: A phase 1/11 randomized control trial (SEOT study)	Assess the safety and effectiveness of ozone therapy as an adjunct to the standard of care for COVID-19.	Unicentric
15	Bahrami, Raeissadat, Barchinejad, Elyaspour, Rahimi-Dehgolan <sup>32</sup>	2019	IRAN	Double-blind Controlled Clinical Trial	A/1B	Local ozone (O <sub>2</sub> -O <sub>3</sub> ) versus corticosteroid injection efficacy in plantar fasciitis treatment: a double-blinded RCT	Compare the effectiveness of local injection of ozone versus corticosteroids in the treatment of fasciopathy.	Absence of a control group; high rate of discontinuity during follow-up (12%)
16	Ercalik, Kilic <sup>33</sup>	2020	TURKEY	Double-blind Controlled Clinical Trial	A/1B	Efficacy of Intradiscal Ozone Therapy with or without Perforaminal Steroid Injection on Lumbar Disc Herniation: A Double-Blinded Controlled Study	Determine the effectiveness of perforaminal steroid injection in conjunction with intradiscal ozone therapy.	Limited sample size and follow-up time
17	Noori-Zadeh, Bakhtiyari, Khooz, Haghani, Darabi <sup>34</sup>	2019	IRAN	Systematic review	A/1A	Intra-articular ozone therapy efficiently attenuates pain in knee osteoarthritic subjects: A systematic review and meta-analysis	Assess the effectiveness of intra-articular ozone therapy for pain relief in knee osteoarthritic subjects.	Heterogeneity in ozone applications, concentration, time of pain assessment; and gender differences
18	Sconza, Respizzi, Virelli, Vandembulcke, Iacono, Kon, et al. <sup>35</sup>	2020	ITALY	Systematic review	A/1A	Oxygen Ozone Therapy for the Treatment of Knee Osteoarthritis: A Systematic Review of Randomized Controlled Trials	Review the literature on the effectiveness of intra-articular ozone therapy for pain relief in knee osteoarthritis.	Data heterogeneity to apply meta-analysis; low quality of the clinical studies analyzed; excess of bias
19	Javadi Hedayatabd, Kachooei, Chaharjouy, Vaziri,	2020	IRAN	Systematic review	A/1A	The Effect of Ozone (O <sub>3</sub> ) versus Hyaluronic Acid on Pain and Function in Patients with Knee Osteoarthritis: A Systematic Review and Meta-Analysis	Compare the effect of ozone versus hyaluronic acid application in reducing pain in patients with knee osteoarthritis.	Inclusion of CE with low level of evidence



	Mehrad-Majd, Emadzadeh, et al. <sup>36</sup>							
20	Izadi, Cegolon, Javanbakht, Sarafzadeh, Abolghasemi, Alishiri, et al. <sup>37</sup>	2021	IRAN	Scoping Review	A/1A	Ozone therapy for the treatment of COVID-19 pneumonia: A scoping review	Review the evidence on the potential application of ozone to treat/prevent severe forms of COVID-19.	-
21	Hernández, Viñals, Pablos, Vilás, Papadakos, Wijeyesundera, et al. <sup>38</sup>	2021	SPAIN	Case-Control Study	B/3B	Ozone therapy for patients with COVID-19 pneumonia: Preliminary report of a prospective case-control study	Determine whether ozonated autohemotherapy was associated with a shorter time to clinical improvement in patients with COVID-19.	Small and unicentric sample size
22	Tascini, Sermann, Pagotto, Sozio, De Carlo, Giacinta, et al. <sup>39</sup>	2020	ITALY	Case-Control Study	B/3B	Blood ozonization in patients with mild to moderate COVID19 pneumonia: a single centre experience	Evaluate the anti-inflammatory and immunomodulatory action mediated by ozone in patients hospitalized for SARS-CoV-2.	Lack of viral load data to confirm the antiviral effects of O2/O3 therapy
23	Fernández-Cuadros, Pérez-Moro, Albaladejo-Florin, Álava-Rabasa <sup>40</sup>	2020	SPAIN	Quasi-experimental	B/2C	El ozono intrarticular modula la inflamación, mejora el dolor, la rigidez, la función y tiene un efecto anabólico sobre la artrosis de rodilla: estudio cuasiexperimental prospectivo tipo antes-después, 115 pacientes	Verify the effect of ozone through pain scores, biochemical data and radiological parameters in a series of patients with knee osteoarthritis.	Lack of randomization
24	Franzini, Valdenassi, Ricevuti, Chirumbolo, Depfenhart, Bertossi, et al. <sup>41</sup>	2020	ITALY	Multiple Cases	A/1C	Oxygen-ozone (O <sub>2</sub> -O <sub>3</sub> ) immunocellular therapy for patients with COVID-19. Preliminary evidence reported	Assess the potential effectiveness of a new approach to treating COVID-19 patients using the oxygen-ozone mixture.	Reduced sampling

Note: COVID-19 - Coronavirus Disease – 2019; O2 – Oxygen; O3 - Ozone; REC/EVI: Degree of Recommendation / Level of Evidence; SARS-CoV-2: Severe Acute Respiratory Syndrome Coronavirus 2.

Next, the Oxygen-Ozone therapy in the analyzed studies is explained in greater detail.

#### In skin lesion caused by ectoparasite bite

Rowen<sup>19</sup> published a case of an acute bacterial infection resulting from a tick bite, which responded immediately to ozone therapy and was completely resolved within 48 hours.

#### Complementary therapy in assisted reproduction

In a case study carried out in the United States<sup>20</sup>, the authors used ozone therapy to improve endometrial thickening in patients undergoing assisted reproduction, thus ensuring better conditions and chances of embryo implantation. The results showed that in the three patients, there was an improvement in the thickness of the endometrial lining, and two of them continued with pregnancy after implantation of a single embryo.

#### Treatment of wounds resulting from complications of diabetes mellitus

Chinese researchers<sup>21</sup> reported a case of a patient with a diabetic hallux wound, with vascular disease of the lower extremity of the limb, who underwent amputation of the hallux and subsequent ozone therapy (bagging for 20

minutes at a concentration of 30mg/L). Consequently, the wound showed good growth of granulation tissue, remained decontaminated and, with adjacent tissues in good condition for secondary surgical suture.

Brazilian researchers<sup>24</sup> reported the case of a 62-year-old patient with type II Diabetes Mellitus (using insulin) who had, for seven months, a lesion in the left lower limb, of traumatic origin and difficult to heal. The patient underwent 15 sessions of ozone therapy (bagging), which took place three times a week for one month and nine days. Microbiological analysis was performed on the first day and on the last day of treatment. In the first one, *Pseudomonas aeruginosa* was detected, a gram-negative bacterium that can present multidrug-resistant strains, with a colony count greater than 100,000/CFU. At the end of the treatment, the microbiological analysis showed a value of 350/CFU, demonstrating the impact of the antimicrobial action of O<sub>3</sub>.

#### Complementary treatment of abscesses and septic infections

An American case report showed the case of a 68-year-old woman with an infected hip prosthesis, whose conventional treatment would have been a succession of surgical procedures such as removal of the prosthesis and implantation of an antibiotic-impregnated spacer. In



addition, the patient would undergo intravenous antibiotic therapy for several months. The patient herself opted for Ozone Therapy, whose protocol consisted of 10 sessions of AHTM, with an O<sub>3</sub> concentration of 70mg/L; and, local applications of 20ml of the O<sub>2</sub>/O<sub>3</sub> mixture, at a concentration of 47mg/L. In view of the result of the culture of the infection secretion, she was prescribed an oral antibiotic (amoxicillin + clavulanic acid). After 2 months, there was a substantial improvement in the infection and in the clinical picture, without the need for invasive procedures<sup>18</sup>.

Chinese researchers<sup>29</sup>, when comparing the effectiveness of percutaneous drainage treatment versus percutaneous drainage associated with Ozone therapy in the treatment of Pyogenic Liver Abscess, they observed that patients treated with Ozone had a shorter febrile time and less need for subsequent surgical intervention.

### Pain management in herniated discs

Clinical trial developed in Turkey<sup>26</sup>, selected 63 patients with low back pain and lumbar disc herniation (documented by MRI) to be treated with intradiscal ozone therapy, with pain scores (using the Visual Analogue Scale - VAS) greater than or equal to 4 for at least eight weeks and that did not respond to conservative treatment. They were submitted to medical ozone application sessions at 25 µg/ml, the pain score was monitored during the interventions and reduced: from 6.96 (pre-procedure value) to 4.25 in one month after the intervention ; to 4.33 three months later; to 4.87 after six months; and, for 5.22, up to 24 months after. The value of  $p < 0.05$  occurred when the values of pre- and post-procedure pain scores were compared. With these results, the authors stated that intradiscal application with the O<sub>2</sub>/O<sub>3</sub> mixture is a minimally invasive and inexpensive procedure that reduces intradiscal inflammation. According to the Macnab criterion, by which the research participants evaluated the success of the outcome of ozone therapy for pain relief, the following results were obtained: Excellent (complete disappearance of symptoms, complete recovery from work activities and sports) – 6.3%; Good (occasional episodes of mild pain) – 26.9%; Sufficient (improvement of symptoms, but physical limitation for daily activities) – 20.6%; Insufficient (partial improvement of symptoms and periodic use of analgesics) – 20.6%; No results (no improvement in symptoms and need for surgical intervention) – 17.46%; and, Negative (worsening of symptoms and need for surgical intervention) – 6.3%.

In an Egyptian study, 52 patients, aged between 27 and 87 years, with symptomatic lumbar disc herniation, without severe degenerative disc changes, who failed conservative treatment, were included. The patients underwent intradiscal injection of the O<sub>2</sub>/O<sub>3</sub> mixture (27 to 30 µg/ml), guided by fluoroscopy (5 ml), shortly after, a periradicular injection of the same O<sub>2</sub>/O<sub>3</sub> mixture (10 ml) associated with steroid ( 1 ml) and local anesthetic (1 ml). According to the pain intensity score, there was a significant decrease in pain intensity in 76% of patients, a proportion that increases to 78% in the 6-month control. To Egyptian

researchers<sup>27</sup> O<sub>2</sub>/O<sub>3</sub> therapy is a simple, economical and safe, technical and minimally invasive method for the treatment of pain due to herniated discs, with a short recovery period. It can be considered as an intermediate treatment option between the failure of conservative treatment and surgery.

In a Chinese clinical trial<sup>30</sup>, the authors included 80 patients with lumbar disc herniation in a Clinical Study with four groups: Group 1 - control; Group 2- Medical ozone with low concentration (20mg/L); Group 3- Medical ozone with moderate concentration (40mg/L); and, Group 4- Medical ozone with high concentration (60mg/L). The results showed that all patients treated with ozone had disc retraction between 6 and 12 months of follow-up. Those who received moderate concentration of Ozone had a higher rate of disc retraction when compared to the other groups. Serum levels of Interleukin-6 (IL-6), Immunoglobulin-M (IgM), Immunoglobulin-G (IgG) decreased significantly, as well as the pain score by VAS. While the activity of the antioxidant enzyme Superoxide Dismutase (SOD) increased in all groups over time ( $p=0.05$ ). The researchers claim that lower concentrations of Ozone (between 20 – 40mg/l) reduce the serum expression of IL-6, IgM, IgG, showing analgesic and anti-inflammatory effects. Moreover, the concentration of 40 mg/ml demonstrated optimal efficacy for the treatment of lumbar disc herniation.

### Management of chronic pain in knee osteoarthritis

In a Systematic Review with Meta-analysis of 10 studies, carried out in Iran<sup>34</sup>, it has been shown that intra-articular ozone therapy is effective for the management of chronic pain in patients with knee osteoarthritis.

Italian researchers<sup>35</sup> when conducting a Systematic Review of clinical trials, focusing on the use of medicinal ozone for knee osteoarthritis, they pointed out that the safe approach generates encouraging effects in pain management and functional recovery in the short and medium term. However, they were faced with low methodological quality of the studies because most of them contain relevant biases of different types, such as selection (sampling and allocation); information (data selection, blinding of participants and evaluators, hiding of results, incomplete results); and confounding factor. Which severely limit the possibility of drawing reliable conclusions from Ozone Therapy to the detriment of other treatments.

In a quasi-experimental study<sup>40</sup>, carried out in Spain, with 115 patients with knee osteoarthritis, the authors emphasize that inflammation biomarkers such as ESR (Erythrocyte Sedimentation Velocity) decreased from 14.52 mm/h to 13.08 mm after O<sub>2</sub>/O<sub>3</sub> therapy ( $p=0.0014$ ). CRP (C-Reactive Protein) was from 0.42 mg/dl to 0.31 mg/dl ( $p=0.0142$ ). Uric acid also had decreased values after treatment, however without statistical significance. Regarding the severity of symptoms (pain, stiffness and function) in knee arthrosis, measured by the Visual Analogue Scale (VAS) of pain, it started from a mean value prior to treatment of 7.11 and reduced to 3.56. According to the Western Ontario and McMaster Universities (WOMAC) quality of life scale, ozone therapy improved pain





( $p=0.0000$ ), stiffness ( $p=0.0000$ ) and function ( $p=0.0000$  variables).

Systematic Review with meta-analysis, developed by Iranian researchers<sup>36</sup>, aimed to compare the effect of Ozone with that of Hyaluronic Acid (HA) to reduce pain and increase function in patients with knee osteoarthritis. With the analysis of 6 randomized clinical trials, no significant difference was detected between treatment with ozone and HA, although the general results have favored HA over ozone.

#### **Analgesia (use of ozone as monotherapy, associated with and/or compared to other anti-inflammatory agents)**

An Italian study used systemic ozone therapy in 65 patients with fibromyalgia: 55 of them received Major Autohemotherapy (AHTM) and Rectal Insufflations, twice a week in the first month, and then twice a month, as maintenance therapy. The authors do not clarify the ozone concentrations used in the study, but they state that they were applied in accordance with the Italian Scientific Society for Oxygen Ozone Therapy. About 70% of patients reported improvement in symptoms<sup>28</sup>. Brazilian researchers<sup>42</sup> emphasize that research whose concentrations, routes of administration and frequency of application of therapeutic ozone are unclear, provide dubious results, subject to questioning and delegitimize the consolidation of ozone therapy in clinical practice.

Case report of an 11-year-old girl, developed in the United States<sup>22</sup>, diagnosed with Reflex Sympathetic Dystrophy (RSD) who had extreme pain in the lower limbs, concomitant with seizures. He used several opioids, without success. She was then treated with Ozone Therapy for 26 weeks. She received 5 weekly sessions initially with 5ml of the O2/O3 blend at a concentration of 55mg/L, being gradually increased until reaching a volume of 30ml, maintained at 55mg/L. After the first sessions, there was a significant improvement in pain and a reduction in the frequency of convulsive activities. After 3 months these convulsive activities became rare. Until they were completely eliminated after the fourth month of treatment, when the pain also disappeared. After 120 Ozone Therapy sessions, the child returned to school, without symptoms of RSD.

Double-blind randomized clinical study with 44 patients with plantar fasciopathy, in Group 1 ( $n=23$ ), participants received local injection of 40mg of methylprednisolone, while in Group 2 ( $n=21$ ) received local application of Ozone at a concentration of 15mg/ml. The evaluations took place before the application and, in 1, 4, 12 weeks after, using the VAS scale. According to the results presented by Bahrami et al.<sup>32</sup>, both treatments efficiently relieved patients' pain and improved their function at 1 and 3 months follow-up. Pain reduction occurred in more than 50% of the patients, and there was an improvement in functional status in 30%. The authors point out that mixing O2/O3 has no side effects, as corticosteroids do.

Turkish researchers<sup>33</sup> also treated patients with low back pain and lower limb pain associated with lumbar disc herniation, performing a Randomized Clinical Trial. Group 1

( $n=35$ ) received therapy with the application of intradiscal O2/O3 mixture (05ml with a concentration of 40  $\mu\text{g/ml}$ ), while Group 2 ( $n=30$ ) received the same intradiscal O2/O3 therapy, with the addition of corticosteroid injection (dexamethasone). For analysis, they used the Oswestry Disability Index (ODI), a scale for functional assessment of the lumbar spine that incorporates measures of pain and physical activity in its score<sup>43</sup>. The mean ODI of Group 1, one month after application, was significantly lower than that of Group 2 ( $p=0.003$ ). They concluded that there was no additional benefit with the inclusion of corticosteroids associated with O2/O3. Indicating that exclusive intradiscal therapy with O2/O3 mixture was sufficient to modulate lumbar and lower limb pain associated with lumbar disc herniation.

Italian study<sup>25</sup> reported the case of a 73-year-old female patient, diagnosed with Facet Joint Syndrome, complaining of low back pain and a history of using tapentadol and pregabalin for pain relief. The patient was submitted to the application of the mixture O2/O3, at 20mg/L associated with aquatic rehabilitation - after the first week of treatment, twice a week, for four weeks. After two weeks of treatment, it was possible to discontinue the use of analgesics due to the improvement of pain symptoms. The authors emphasize that rehabilitation with aquatic exercises contributed to the maintenance of the results obtained with Ozone Therapy.

#### **Management of COVID-19**

In a study carried out in Spain<sup>23</sup>, the researchers published a report of three cases with rapid improvement of hypoxia and decrease of inflammatory markers (CRP – C Reactive Protein and LDH – Lactate Dehydrogenase) and, D-dimer, immediately after 1 to 4 sessions of systemic ozone therapy, in patients with COVID-19 who had respiratory failure. Two sessions of AHTM were performed, at 40  $\mu\text{g/ml}$ , for 3 consecutive days, with an interval of 12 hours between applications. This report shows that the three patients did not require invasive ventilation after Ozone Therapy and all were discharged home early after 4-6 sessions of Autohemotherapy.

Italian researchers<sup>41</sup> evaluated the potential effectiveness of O2/O3 blend therapy, through a case series study, to treat patients with COVID-19. Cycles of Ozone Therapy were applied to 50 patients with Severe Acute Respiratory Syndrome (SARS), aged over 60 years, all male and under non-invasive mechanical ventilation. Two research participants died. After four cycles of AHTM, a concentration of the mixture O2/O3 of 45  $\mu\text{g/L}$ , a significant reduction of inflammatory markers such as CRP, IL-6 and D-dimer was observed. In addition, there was an improvement in the main respiratory indices such as peripheral O2 saturation (SpO2), O2 blood pressure (PaO2) and Inspired O2 fraction (FiO2).

Case-Control Study, carried out with 60 participants hospitalized for COVID-19, at the University Hospital of Udine<sup>39</sup>, of which 30 constituted the Intervention Group, treated with AHTM + institutional protocol; the Control Group, also composed of 30 patients, received only the



institutional protocol for the treatment of COVID-19. In the Intervention Group, only about 7% (n=2) of the participants showed clinical worsening, against 17% (n=5) in the Control Group. Of the 60 participants, there were only 02 deaths of participants in the Control Group.

Researchers<sup>38</sup> selected 18 patients with confirmed Sars-CoV-2 infection for a prospective study, Case-control method. Inclusion criteria included pneumonia on chest X-ray, O<sub>2</sub> saturation (SpO<sub>2</sub>) < 94% on room air and tachypnea, respiratory rate greater than 30 breaths per minute. The Case Group received AHTM at a concentration of 40 µg/L twice a day for five consecutive days. The Control Group was treated with oxygen supplementation, hydroxychloroquine, lopinavir/ritonavir, corticosteroids and antibiotics, according to the individualized medical prescription of each participant. Ozonated AHTM was associated with a significant reduction in time to clinical improvement (p=0.04), which was 12.4 days shorter than the control group. In this same study, AHTM was associated with a two-fold shorter time to CRP reduction (p=0.008), ferritin (p=0.16), D-dimer (p=0.009) and LDH (p=0.01) compared to the control group.

In a Randomized Clinical Trial, including 60 patients with mild to moderate NEWS (National Early Warning Score) clinical deterioration, they were divided into two groups for treatment: a) Intervention Group (n=30): Rectal Insufflation with O<sub>2</sub>/ O<sub>3</sub> + Minor Autohemotherapy (AHTm) associated with the institutional protocol for the treatment of COVID-19; b) Control Group (n=30): exclusively received the institutional protocol for the treatment of COVID-19. The results showed that the Ozone Therapy group clinically improved all parameters tested when compared to the control group. Statistical significance was observed only in the negative PCR-RT variable (Reverse-Transcriptase Polymerase Chain Reaction: RT-PCR) with p=0.01, change in clinical symptoms (p=0.05) and need for intensive care (p=0.05). The authors emphasize that the participants in the Intervention Group did not have any need for supplemental oxygen, admission to the Intensive Care Unit (ICU), mechanical ventilation, and there were no deaths. The NEWS score showed greater magnitude in the mean score, thus indicating a lower risk profile for clinical deterioration in this group. In the Control Group, patients underwent mechanical ventilation and required ICU, and 2 patients died<sup>31</sup>.

A Scope Review, developed in Iran<sup>37</sup>, aimed to synthesize the evidence on the application of ozone therapy to treat and prevent severe forms of COVID-19. The authors concluded that this may be a potential resource to modulate the patient's immune response against the SARS-CoV-2 virus, contributing to contain the cellular oxidative stress of COVID-19. Ozone is competent to break the vicious cycle of inflammatory cytokine storm seen in severe forms of the disease. Ozone therapy is also shown to be effective in early cases of COVID-19, preventing the progression of the life-threatening disease.

The results presented are relevant considering the high morbidity and mortality generated by the COVID-19

pandemic, especially in patients undergoing mechanical ventilation. According to the authors, about 15% of infected adult patients develop severe pneumonia, which requires supplemental O<sub>2</sub>, and an additional 5% of these patients progress to Severe Acute Respiratory Syndrome (SARS)<sup>38</sup>.

A limitation of the present study is the fact that it mostly exhibits Case Studies (n=8) to the detriment of systematic reviews (n=4) and Randomized Clinical Trials (n=5).

### Final Considerations

This literature review presented the most recent applications of Ozone Therapy, considering a cut of the last three years, namely: skin lesion by ectoparasite bite; use of ozone as a complementary therapy in assisted reproduction; treatment of wounds resulting from complications of diabetes mellitus; complementary treatment of abscesses and septic infections; pain management in herniated discs; chronic pain management in knee osteoarthritis; use of ozone for analgesia (being used as monotherapy, associated and/or compared to other anti-inflammatory agents); and in the management of COVID-19. It is noteworthy that none of the studies showed adverse reactions related to the O<sub>2</sub>/O<sub>3</sub> mixture.

Considering the overwhelming scenario of the COVID-19 pandemic, it is extremely relevant that a therapy has shown results of significant improvement of inflammatory markers (IL-6, CRP) and D-dimer, reducing the pulmonary inflammatory process, ICU admissions and mortality, as did Oxygen-Ozone Therapy.

In addition to the pandemic, global health is also facing a crisis in the management of infectious diseases, which are on the rise. Despite the development of new antibiotics and antifungals, the control of superbacteria/fungal infections is still an unresolved issue. The spread of resistant bacteria and fungi, due to the widespread use of antibiotics and antifungals, and the progressive increase in the number of resistant strains has become a global health concern. The mixture of gas with Ozone, as it has bactericidal and antifungal properties, without causing resistance, can be applied as a new countermeasure against infections and has an important effect in the adjuvant treatment of several diseases.

The implementation of Therapy with the O<sub>2</sub>/O<sub>3</sub> mixture in Brazil has gained many supporters and has slowly become accessible in the Unified Health System, as well as in the supplementary system. In order for it to be recognized and used on a large scale, it is still necessary to follow a path of training, legalization and regulation of the practice, permeated by research whose methods generate the best levels of evidence and degrees of recommendation.

Finally, as an integrated and complementary therapeutic approach to orthodox medicine, recent and innovative in the Brazilian scenario, Ozone Therapy is potent to be applied in situations of specific morbidities, in different scenarios.



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