Review

ADJUVANT OZONE THERAPY IN KNEE OSTEOARTHRITIS: A LITERATURE REVIEW

D. Livella

Orthopedic Service, Clinical Institute "Città di Brescia", Brescia, Italy

**Correspondence to*:
Delia Livella, MD
Orthopedic Surgeon,
Orthopedic Service,
Clinical Institute "Città di Brescia",
Via Bartolomeo Gualla 15,
25128 Brescia, Italy
e-mail: livella.delia@gmail.com

ABSTRACT

The aim of this work is to evaluate data from the literature from 2013 to date on the application of oxygen-ozone therapy in the treatment of knee osteoarthritis to assess its therapeutic potential in comparison with other non-surgical treatment options.

KEYWORDS: *oxygen, ozone, therapy, osteoarthritis, knee, cartilage, degeneration*

INTRODUCTION

Osteoarthritis (OA) is defined as a degenerative joint condition of unknown etiology, which can be mono- or polyarticular in onset and is progressive in nature. It is characterized by alterations in articular cartilage and reactive bone formation at the subchondral level and the articular margins. The pathology is marked by progressive cartilage degeneration (where cartilage becomes softened and thins until complete erosion occurs, exposing the underlying bone), formation of periarticular osteophytes, and synovial and capsular inflammation. Clinical manifestations of OA include pain, functional limitation, joint swelling, and deformity. OA is associated with chronic joint inflammation that causes persistent oxidative stress (1, 2).

OA is a highly debilitating condition with significant socio-economic impact. The World Health Organization (WHO) estimates that globally, 25% of adults over the age of 25 experience pain and disability associated with this disease. It is one of the most prevalent and disabling conditions, affecting both sexes (with a higher incidence in females). The prevalence significantly increases after the age of 55. Although OA predominantly affects the elderly, younger individuals are not spared, and this disease is the leading cause of lost workdays.

Only 10-20% of individuals with radiological evidence of the condition exhibit signs and symptoms of the disease. OA affects women more frequently than men, particularly evident after the age of 55 when the highest number of OA cases is reported; prior to this, especially until the age of 45, OA affects men more frequently. Between the ages of 45 and 55, the incidence is almost equal in both sexes. The early onset in men may be attributed to occupational activities. At the same time, the more common occurrence in women after 55 may be linked to osteometabolic alterations related to post-menopausal hormonal changes (1, 2).

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Degenerative lesions affecting the joints are numerous and involve the cartilage, subchondral bone, and tendon insertions. Frequently, the degenerative process can be complicated by phases of joint inflammation, leading to swelling with effusion.

OA can be classified into primary forms, often affecting multiple joints, and secondary forms, which are more frequently localized. Primary OA has a genetic predisposition, and it is not uncommon to observe it in multiple family members. Secondary OA can also affect younger individuals and is often associated with trauma, obesity, malformations of the lower limbs, occupational exposures (such as using vibrating tools or repetitive tasks in non-physiological positions), and arthritis, among others.

The International Cartilage Repair Society (ICRS) classifies OA into four grades:

- Grade 0 (normal);
- Grade 1 (nearly normal: superficial lesion);
- Grade 2 (abnormal: lesion extending to 50%);
- Grade 4 (very abnormal: osteochondral lesion).

The most common symptom reported by patients with OA is pain, which worsens with activity and decreases with rest. As the disease progresses, symptoms may include stiffness, reduced joint range of motion, episodes of swelling due to joint effusion, and a grinding sensation during movement, leading to joint deformities (varus or valgus deviation in the knee).

Pain is the primary symptom that prompts patients to seek medical care. Diagnosis is based on the radiological appearance, which also helps determine the stage of the disease (1). Treatment is closely related to the clinical condition of the patient and is most effective and least invasive when initiated early. Traditionally, it consists of physical therapy (including exogenous and endogenous thermotherapy, massage therapy, cryotherapy, and electrotherapy), pharmacological therapy (NSAIDs, analgesics, adjuvants), intra-articular infiltrative therapy (corticosteroids, NSAIDs, hyaluronic acid, platelet-rich concentrates, anesthetics), and surgical therapy (arthroscopy, joint replacement surgery).

Infiltrative therapy is indicated for the treatment of all inflammatory (non-infectious) and degenerative joint conditions, including joint diseases (OA, arthritis) and soft tissue conditions (capsulitis, tendinitis, tenosynovitis, bursitis, fascitis, radicular syndromes, among others) (2).

The biological effects of ozone, such as anti-inflammatory action, anti-edematous effects, analgesic action, enhancement of and activation of microcirculation, tissue regenerative action, a direct effect due to its high oxidative potential, activation of cytokines and phagocytosis, and immunomodulation, indicate a rational and judicious use of ozone in appropriate and calibrated concentrations and quantities, with suitable routes of administration and under correct modalities, in combination with other substances (such as hyaluronic acid, collagen, PRP) for the treatment of knee osteoarthritis (3-9).

MATERIALS AND METHODS

The keywords used as search criteria were ozone therapy, medical ozone, knee osteoarthritis, hyaluronic acid, systematic review, meta-analysis, edited from January 2014. Scientific articles were obtained through PubMed, Embase, Cochrane, and ResearchGate. Preference was given to systematic reviews and meta-analyses. Additional consultation was made of orthopedic texts regarding the treatment of knee osteoarthritis and texts on oxygen-ozone therapy.

RESULTS

The common consideration across the evaluated studies, particularly the systematic reviews and meta-analyses, is the relative methodological quality observed in the analyzed articles, which partially affects the validity of the evidence regarding the efficacy of oxygen-ozone therapy in the treatment of knee osteoarthritis.

The eligibility criteria and subsequent inclusion of the articles reviewed led to a significant reduction in the available literature; thus, only 7 papers were selected (3-9).

DISCUSSION

Raeissadat et al. (3) identified a total of 231 articles, ultimately including 7 studies in their qualitative review (544 patients) and 5 studies (428 patients) in their quantitative analysis. Sconza et al. (4) included 11 studies (858 patients) from a pool of 116, while Arias-Vásquez et al. (5) selected 8 studies (335 patients) from 93.

The authors agree on the effectiveness of oxygen-ozone therapy in reducing pain associated with knee osteoarthritis, with results showing greater efficacy than placebo or non-invasive treatments. The therapy demonstrated results comparable to those of hyaluronic acid or platelet-rich plasma (PRP) in cases of moderate osteoarthritis (grades 1-3) and was noted to reduce pain more rapidly, particularly in short to medium-term (1-3 months) while also improving joint functionality. However, the long-term outcomes reported in the analyzed studies varied considerably.

Experimental studies on rats (6) demonstrated the non-toxicity of ozone injections in cartilage, comparing the effects histologically with mono-iodoacetate (MIA). These authors subsequently induced osteoarthritis in the knees of rats using MIA, which was treated with 50 µml of ozone at 30 micrograms/ml in the right knee and pure oxygen in the left knee, administered three times a week for three weeks. Histological evaluations conducted after the final administration revealed a beneficial effect on cartilage from the ozone injection after 8 days, with progressively diminishing effects noted in evaluations after 11 and 15 days post-injection, although still superior to oxygen injection.

The assessment of ozone efficacy compared to hyaluronic acid (7) did not reveal significant differences between the groups in pain reduction, improved stiffness, or functional enhancement. The combination of both treatments showed a significantly better outcome, particularly at the 2-month follow-up in patients with knee osteoarthritis, compared to treatment with only ozone or only hyaluronic acid (8).

Additionally, a comparison between PRP and ozone administration (9) demonstrated that both substances contributed to pain reduction, functional recovery, and improved quality of life. Ozone appeared more effective for intense pain relief, while PRP showed greater and more lasting effects on pain reduction and functional recovery. The combination of both treatments did not significantly alter the overall results.

CONCLUSIONS

Knee osteoarthritis is among the most prevalent musculoskeletal diseases. While symptoms may remain mild and stable over long periods, they are primarily associated with the degeneration of the articular cartilage. The condition also involves the formation of osteophytes, weakening of the subchondral bone, synovial inflammation, and alterations in the surrounding ligaments, tendons, and muscles.

Cartilage degeneration is triggered by elevated levels of inflammatory cytokines, which increase oxidative stress and metalloproteinase activity. Treating knee osteoarthritis with ozone is considered a safe and effective therapy due to its ability to activate Nrf2 (a signaling transducer), downregulate NF-kB, and modulate the NLRP3 inflammasome. The Nrf2 domain is responsible for activating the transcription of antioxidant response elements. The anti-inflammatory effect inhibits NF-kB, which activates pro-inflammatory cytokines such as TNF-alpha, IL-1 beta, and IL-8. Heme oxygenase-1, activated by Nrf2, inhibits NF-kB, thus blocking the pro-inflammatory cascade. Heme oxygenase-1 can also directly activate anti-inflammatory cytokines and increase endothelial progenitor cells. Furthermore, ozone treatment may diminish inflammation mediated by NLRP3, enhancing the antioxidant activity of Nrf2 and inhibiting apoptosis.

The correct selection of concentrations and appropriate volumes, the executor's skills, the use of suitable equipment, and adherence to hygiene and safety standards are essential elements for successful treatment. Literature indicates that the safest, sufficient, and most effective ozone concentrations range between 10 and 50 µml, with maximum anti-inflammatory effects observed at concentrations between 30 and 45 µml.

The duration of therapy typically varies from 6 to 10 weeks, with 1 to 3 sessions per week, depending on the patient's age, symptom severity, and disease stage. The use of ultrasound support can enhance effectiveness and precision, particularly in peri-articular and tendinous infiltrations.

There is an evident need for more precise, comprehensive, and exhaustive scientific evidence to consolidate the safety of ozone utilization and to develop further improved guidelines.

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