

Combined Therapy of Hyaluronic Acid and Intra-Articular Ozone in Knee Osteoarthritis

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Abstract

Knee osteoarthritis is a common cause of pain and disability in older adults. Among intra-articular therapies, Visco supplementation with hyaluronic acid (HA) and oxygen-ozone therapy (O_3/O_2) have shown analgesic and functional effects. Recent studies suggest that combining HA and ozone may provide complementary benefits: HA improves the viscoelastic properties of synovial fluid and modulates mechanical inflammation, while ozone exerts analgesic, antioxidant, modulating, and immunomodulatory effects at the synovial level. This article reviews the pathophysiology, mechanisms of action, and available clinical evidence and proposes a practical protocol for their combined use in clinical practice.

Keywords: Knee Osteoarthritis; Hyaluronic Acid (HA); Oxygen-Ozone Therapy (O_3/O_2)



Introduction

Knee osteoarthritis (gonarthrosis) affects the integrity of the cartilage, synovial membrane, and periarticular structures, resulting in pain, stiffness, and functional limitations. Treatment options range from non-pharmacological measures and analgesics to intra-articular therapies and arthroplasty. Intra-articular injections offer a therapeutic bridge, especially useful for patients who do not wish to undergo

or are not immediate candidates for surgery. Two interventions that have gained interest in the last decade are viscosupplementation with hyaluronic acid (HA) and intra-articular oxygen-ozone therapy (O_2/O_3) [4].

Brief pathophysiology and therapeutic target

Osteoarthritis involves cartilage degradation, altered synovial fluid (decreased viscosity), low-grade inflammation, and local oxidative stress. Treating the loss of viscoelasticity (with hyaluronic acid) and modulating inflammation/oxidative stress (with ozone) are complementary strategies that address different pathogenic axes: mechanical/viscoelastic and biochemical/oxidative.

Mechanisms of action

Hyaluronic acid (HA)

- Restores the viscoelasticity of the synovial fluid, improves lubrication and mechanical cushioning.
- It modulates the synovial inflammatory response (reduction of pro-inflammatory cytokines) and promotes cartilage homeostasis.
- Indirect analgesic effect by reducing mechanical stress and inflammation.

Evidence of the effectiveness of HA versus placebo shows small but clinically relevant reductions in pain and function in various studies and meta-analyses.

Ozone (O_2/O_3) intra-articular

- Ozone is an oxidizing agent that, in controlled therapeutic concentrations, induces a hormetic redox response: it stimulates endogenous antioxidant systems (glutathione, antioxidant enzymes), reduces pro-inflammatory mediators, and improves local microcirculation.
- Analgesic effects: Decreased nociceptive sensitization and modulation of cytokines.
- Clinical studies have documented improvement in pain and function after intra-articular ozone injections [2].

Biological rationale for the combination

Combining hyaluronic acid (HA) and ozone aims to achieve a synergistic effect: HA restores the biomechanical environment and provides a mechanical-protective effect, while ozone acts on inflammation, oxidative stress, and pain. Preliminary studies and clinical series suggest that the combination may improve outcomes compared to either therapy alone, although large, long-term, multicenter randomized controlled trials (RCTs) are lacking.

Clinical evidence

Ozone vs placebo or comparative studies

Lopes de Jesus, *et al.* (*PLoS One*, 2017) [1] demonstrated that intra-articular ozone injections improved pain and function versus placebo, in a randomized, double-blind trial.

Studies on hyaluronic acid

Systematic reviews and meta-analyses show that Visco supplementation with hyaluronic acid (HA) produces a moderate reduction in pain and functional improvement in knee osteoarthritis, although the effect size and duration vary depending on the product (molecular weight), injection regimen, and severity of OA. *BMJ* and recent reviews summarize these findings [5].

Studies on the combination AH + ozone

Retrospective series/observational studies (e.g. Shahinpour, *et al.* 2023) [3] report significant improvement in pain and function after injecting high molecular weight hyaluronic acid combined with ozone, with no major adverse events reported. These studies suggest benefit but, by design, do not prove causality with the strength of a randomized controlled trial.

Recent controlled trials (2024 - 2025) [6] and preliminary articles indicate that the combination may provide greater pain relief and improved quality of life compared to monotherapy in the short to medium term, although follow-up data at 12-24 months and robust cost-effectiveness evidence are lacking. Clinical studies from 2025 point to promising results that require replication.

Suggested practical protocol for CUBAZALUD

The following is a proposed pragmatic protocol, based on the literature and reported clinical practices. It should be adapted to local regulations, informed consent, and the team's experience.

Patient selection

- Symptomatic gonarthrosis of grade I-III (Kellgren-Lawrence radiological), mechanical/inflammatory pain with functional limitation.
- Contraindications: Active joint infection, neoplasia in the area, known allergy to components, uncontrolled systemic inflammatory state, unmanaged anticoagulation (assess risk).
- Explain palliative/modulating nature and realistic expectations.

Materials

- High molecular weight HA (depending on availability: for example, 1 single injection of 60 mg Hylan GF 20 or a regimen of 3 - 5 injections depending on the product).
- Ozone equipment: certified clinical generator, O₂/O₃ gas with concentration control.
- 22G-25G needles for intra-articular infiltration, aseptic technique, ultrasound (recommended) for guidance.

Technique (combined proposal)

Option A - Sequential injection in the same session (frequently used in publications):

1. Preparation and asepsis. Consent and local antisepsis.
2. First injection: Intra-articular ozone.
 - Suggested concentration: 10-20 µg/mL (varies according to protocol; in some RCTs 10-30 µg/mL were used).
 - Volume: 5-10 mL of O₂/O₃ mixture.
 - Slow injection; wait 2-3 minutes after injection.
3. Second injection: Hyaluronic acid.
 - Inject HA immediately after ozone (in the same session) or wait 5-10 minutes according to clinical preference.
 - AH regimen: According to product (e.g. 1 single high-concentration dose or a 3-injection weekly regimen).

4. Relative rest and observation 30-60 minutes.
5. Repetition: If a regimen is chosen, repeat sessions at intervals according to the HA product and ozone protocol (some protocols involve 3 weekly ozone sessions and 1-3 distributed HA injections). Evidence for combination therapy is heterogeneous; a pragmatic guideline is: 1 initial combined session and 1-2 ozone booster sessions at 2-4 weeks.

Monitoring and follow-up

- Evaluate pain (VAS), WOMAC or IKDC and function at 1, 3 and 6 months.
- Record local adverse events (post-procedure pain, effusion, infection).
- Repeat image (if necessary) only as clinically indicated.

Safety and adverse effects

- Both procedures are relatively safe when applied with aseptic technique and certified generators/products.
- Transient reactions: Post-injection pain, local swelling, dizziness. Low risk of joint infection — aseptic protocol essential.
- Ozone: Minimal risk at therapeutic concentrations; avoid gas embolism (use correct technique, do not inject gas at high pressure).
- AH: Transient local inflammatory reactions; rare allergies.

Published studies have not shown a significant increase in serious events in groups treated with ozone or AH, individually or in combination, in available series and RCTs.

Discussion

The combination of hyaluronic acid (HA) and ozone has a sound biological basis and favorable initial evidence. Potential benefits include faster analgesia from ozone and a protective/supportive effect of HA on joint mechanics. However, the quality of evidence varies: there are randomized controlled trials (RCTs) of ozone versus placebo and RCTs of HA versus other injections, as well as series and retrospective studies evaluating the combination; but randomized, double-blind, multicenter trials with long-term follow-up that confirm sustained superiority and cost-effectiveness are still lacking. Furthermore, heterogeneity in ozone concentrations, types of HA, and administration protocols makes direct comparisons difficult.

Implications for CUBAZALUD: Implementing a standardized protocol (with recording of clinical variables and events) allows for the accumulation of local experience and the generation of observational clinical data that could be published as a series or prospective study. Offering the combination as an option to selected patients with realistic expectations can improve satisfaction and functionality, always with informed consent and documented records.

Conclusion

1. The combination of hyaluronic acid and intra-articular ozone is a promising therapeutic option in knee osteoarthritis, addressing both the mechanical component (viscoelasticity) and the biochemical component (oxidative stress/inflammation).
2. The available clinical evidence (trials and series) shows improvement in pain and function, but a greater number of high-quality RCTs and long-term follow-up are still required to establish solid routine recommendations.
3. In practice, a combined protocol, performed with aseptic technique, certified ozone generator and high-quality AH, can be used in selected patients, recording results and adverse effects to evaluate efficacy and safety.

Bibliography

1. Lopes de Jesus CC., *et al.* "Comparison between intra-articular ozone and placebo in the treatment of knee osteoarthritis: a randomized, double-blinded, placebo-controlled study". *PLoS One* 12.7 (2017): e0179185.
2. Raeissadat SA., *et al.* "Intra-articular ozone or hyaluronic acid injection - randomized comparative studies and reviews". *Journal of Pain Research* 11 (2018): 111-117.
3. Shahinpour S., *et al.* "Evaluation of effectiveness of combined intra-articular high molecular weight hyaluronic acid and ozone in knee osteoarthritis". *Acta Medica Iranica* 61.9 (2023).
4. Sconza C., *et al.* "Ozone therapy versus hyaluronic acid injections for pain relief in knee osteoarthritis: randomized double-blind trial and reviews". *International Journal of Molecular Sciences* 24.10 (2023): 8788.
5. Pereira TV., *et al.* "Viscosupplementation for knee osteoarthritis: systematic review and meta-analysis". *British Medical Journal* 378 (2022): e069722.
6. "Studies and reviews 2024-2025 that compare combinations and report promising results (controlled trials and synthetic analyses)".

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