

Ozone therapy for musculoskeletal disorders: Current concepts

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Summary. Medical ozone O₃ therapy combines a mixture of oxygen (O₂)-O₃ and prepared through conversion of pure O₂ into O₃ using special medical generators. O₃ has multiple mechanisms of action: analgesic, antiinflammatory, and antioxidant effects. These therapeutic effects are obtained by amelioration of tissue oxygenation, accelerating glucose usage in cellular metabolism, improving protein metabolism, increasing erythrocyte activity, inhibiting inflammatory mediators, reducing the synthesis of prostaglandins and decreasing joint oxidative stress. O₂-O₃ has been proved to be effective in reducing pain in many musculoskeletal disorders including low back pain, lumbar disk herniation, cervical pain, cervical disk herniation, failed back surgery syndrome, degenerative spinal disease, knee osteoarthritis, meniscal injuries, sacroiliitis, plantar fasciitis and carpal tunnel syndrome, with rare adverse effects if judiciously used according to precisely defined guidelines. (www.actabiomedica.it)

Keywords: Medical ozone ; pain therapy ; low back pain ; cervical pain ; osteoarthritis

Introduction

Ozone (O₃) gas is highly water soluble and consists of three oxygen molecules (1). Medical O₃ therapy combines a mixture of oxygen (O₂)-O₃, with a therapeutic range not exceeding 40 µg of O₃ per ml of O₂ and prepared through conversion of pure O₂ into O₃ using special medical generators (2). In orthopedic field, O₂-O₃ can be administered through several ways: subcutaneous, intramuscular, intra-articular, intradiscal, intraforaminal, periganglionic and periradicular (1,3). The main restrictions for the use of O₂-O₃ are: pregnancy, hyperthyroidism, thrombocytopenia, and ozone allergy (4).

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mediators, reducing the synthesis of prostaglandins and decreasing joint oxidative stress (5,6).

A large number of studies have confirmed the efficacy and safety of O₂-O₃ therapy in the treatment of many musculoskeletal diseases including low back pain (LBP), lumbar disk herniation, cervical pain, cervical disk herniation, failed back surgery syndrome, degenerative spinal disease, knee osteoarthritis (KOA), meniscal injuries, sacroiliitis, plantar fasciitis (PF) and carpal tunnel syndrome (CTS) (6-12). The aim of the present paper is to report the current concepts of the clinical utility of O₂-O₃ therapy for different musculoskeletal disorders.

Low Back Pain

LBP is one of the most prevalent pain disorders. It is estimated that about 80% of the population experience LBP during the course of their life and 55% suffer from

LBP associated with radicular syndromes (7,13). The natural history of LBP is self-limiting, with the majority (80–90%) of patients showing improvement within 6–12 weeks (2). LBP is treated initially by rest, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, muscle relaxants, physiotherapy and weight loss (7). Patients who do not respond to standard conservative treatments may take advantage of O2–O3 therapy which has a good success rate of about 70–80 % (13,14). O2–O3 therapy is a minimally invasive injection for the treatment of LBP which is widely practiced in Europe, Asia and South American countries (15,16). This gas can be injected directly: intradiscal, intraforaminal, periganglionic and periradicular or indirectly in the paravertebral muscles aiming to relieve LBP by disk shrinkage, relieving nerve root compression, ameliorating tissue oxygenation with potential analgesic and anti-inflammatory effects (16–18).

Direct Intradiscal, Intraforaminal, Periganglionic And Periradicular Injections

The rationale for direct O2–O3 therapy is that the patient's pain is caused by mechanical compression of the nerve root associated with periganglionic and periradicular inflammatory responses (19). Intradiscal injection of O2–O3 was first reported in the 1990s (15). Several clinical reports of the use of O2–O3 to treat lumbar (13,15,20) disc herniations in humans have been presented in the literature.

Steppan et al. (15) performed a meta-analysis to estimate the pain, function, and safety outcomes of O2–O3 treatment for lumbar herniated discs. They found that O2–O3 therapy is effective in 70–80% of patients with lumbar herniated discs. Moreover, pain and function outcomes are similar to the outcomes for lumbar discs treated with surgical discectomy, but the complication rate is much lower (<0.1%) and the recovery time is significantly shorter. Magalhaes et al. (20) also performed a systematic review and meta-analysis of randomized controlled trials (RCT) to evaluate the therapeutic effects of percutaneous injection of O2–O3 for LBP secondary to disc herniation. They found that O2–O3 therapy appears to yield positive results and low morbidity rates. Therefore, they concluded

that this method may be considered an option to treat lumbar disc herniation-related LBP that has failed to respond to conservative treatment, representing an alternative to surgery.

Large-sample studies have reported the procedure to be effective in LBP relief in the short term (14) as well as in the long term up to 10 years (21). Buric et al. (21) assessed the clinical and morphological results of 108 patients with confirmed contiguous disc herniation that were treated with intradiscal injection of O2–O3 at a followup of 5 and 10 years. They observed that of the patients that avoided surgery 82% and 88% were improved (better or much better) at 5 years and 10 years respectively.

O2–O3 therapy has been proved to be superior to steroid injection for treatment of LBP. Bonetti et al. (22) performed a RCT to compare the clinical outcomes in 306 patients with acute or chronic low back and sciatic nerve pain treated with intraforaminal O2–O3 or periradicular steroids infiltrations. They observed that short-term (1 week) outcomes were similar in both groups of patients. Whereas medium (3 months) and long-term (6 months) results marginally favored O2–O3 treatment, especially in patients with painful disk disease. Thus, they concluded that O2–O3 treatment was highly effective in relieving acute and chronic LBP and sciatica and the gas mixture can be administered as a first treatment to replace epidural steroids to avoid surgery.

The intradiscal injection can be associated with periganglionic injection of corticosteroid and anesthetic, producing a cumulative effect enhancing the overall outcome of treatment (14,23). Perri et al. (14) performed a prospective randomized double-blind study to evaluate the clinical efficacy of periganglionic steroid and local anesthetic with intradiscal O2–O3 injection versus steroid and local anesthetic intraforaminal injection in 517 patients at a followup of 6 months. They observed that intradiscal O2–O3 and intraforaminal steroid with local anesthesia injections got higher success rates (80%) compared to treatments with only steroid and local anesthetic (31.5%) after follow-up of 6 months in terms of pain reduction. Gallucci et al.²³ prospectively compared the clinical effectiveness of intraforaminal and intradiscal injections of a mixture of a steroid, a local anesthetic, and O2–O3

(Group A) versus intraforaminal and intradiscal injections of a steroid and an anesthetic (Group B) in the management of radicular pain related to acute lumbar disc herniation. After 6 months, they observed that the treatment was successful in 61 (74%) patients in group A and in 36 (47%) patients in group B. Hence they concluded that intraforaminal and intradiscal injections of a steroid, an anesthetic, and O₂-O₃ are more effective at 6 months than injections of only a steroid and an anesthetic.

O₂-O₃ therapy is an ideal treatment with no side-effects also in elderly patients with degenerative spine disease other than disc degeneration. Bonetti et al. (24) assessed the outcome of O₂-O₃ injection in the periganglionic and the region surrounding the facet joint associated with intramuscular paravertebral ozone injections in 129 elderly patients, aged between 65 and 93 years, who had CT or MR evidence of advanced zygo-apophyseal degenerative arthrosis, multiple levels of lumbar disc disease, segmental canal stenosis, pseudo-spondylolisthesis and severe scoliosis at a followup of 3 and 12 months. They observed that at 3 months follow-up 74 (57.3%) patients referred a marked improvement in clinical symptoms with almost complete disappearance of LBP, whereas 32 (24.8%) were satisfied with the treatment but had only a partial reduction of pain. Moreover, at 12 months followup, 43 (33.9%) had maintained an excellent quality of life with an almost complete disappearance of LBP and the number of patients with good or satisfactory benefit after treatment had increased to 34 (26.7%). They concluded that the good results obtained indicate that O₂-O₃ therapy is a valid treatment with no side-effects in elderly patients with degenerative spine disease with contraindications to drug management or concomitant age-related diseases.

Indirect Intramuscular Injections

Indirect injection of O₂-O₃ into the paravertebral muscle adjacent to a herniated disc was first proposed by Verga in 1989 (15). The indirect approach consists of the injection of 10–20 ml of O₂-O₃ gas in one to four sites of the paravertebral muscles in patients with LBP (25). Bocci et al. (26) defined it as

“chemical acupuncture” because both the needle and gas injection have a role in eliciting a complex series of chemical and neurological reactions by stimulating local C-nociceptors and leading to the disappearance of pain in the majority of patients with LBP.

Paoloni et al. (27) conducted a multicenter, double-blind, RCT in 60 patients suffering from acute LBP caused by lumbar disc herniation (LDH), to assess the clinical outcome of intramuscular-paravertebral O₂O₃ injection compared to placebo treatment. They found a significant difference between the 2 groups in the percentage of cases who had become pain-free (61% vs. 33%) at 6 months followup. Özcan et al. (28) compared retrospectively the pre and post treatment pain scores of 62 patients undergoing intramuscular paravertebral O₂-O₃ injections for LBP. They observed a significant improvements of clinical scores between the pre injection and first month controls that were maintained at 3 months followup.

Cervical Pain

Few studies (8, 28) assessed the efficacy of O₂-O₃ therapy for cervical pain. Beyaz et al. (8) investigated the 6-month efficacy and safety of intradiscal O₂-O₃ mixture therapy in 44 patients with cervical disc herniation and chronic neck pain. They observed a 73.1% decrease in the average VAS score compared with the baseline values at the final follow-up. 88.6% of patients were satisfied, 9.1% were moderately satisfied, and 2.3% were poorly satisfied. Alexandre et al. (28) assessed the efficacy of the treatment of 252 patients affected by cervical disc herniation, treated by single intradiscal injection of O₂-O₃ preceded and followed by 5 intramuscular paravertebral injections. They observed that pain symptomatology was completely abolished in 79.3%, sensory dysfunction was abolished in 78.1% and complete regression of motor deficit in 61.9% of cases.

Knee Osteoarthritis

KOA is a degenerative joint disease that lead to a decrease in body function due to pain and stiffness of

the knee (5, 29). Osteoarthritic joints are characterized by cartilage degeneration, subchondral bone sclerosis, osteophytes formation, synovial inflammation, and degeneration of periarticular tissues⁴ leading to pain, stiffness and swelling (30).

There is no definitive cure to stop progression of KOA. However, to alleviate pain and improve function in patients with KOA, several pharmacological and non pharmacological treatments are available. Pharmacological treatments include analgesics, topical and oral NSAIDs and chondroprotectors. Nonpharmacological treatments include weight loss, orthotics and physical therapy (6, 30). For patients who do not respond to conservative treatment and are not a candidate for arthroplasty, different intra-articular injections are available, such as corticosteroids, dextrose, hyaluronic acid (HA), platelet-rich plasma (PRP), and O2-O3 injections (30). In a meta-analysis, Vaquez et al. (6) concluded that intra-articular infiltrations of O2-O3 can be used as an optional effective treatment for the management of pain related to KOA.

It has been confirmed that O2-O3 injection is effective for short-term management (1–3 months) of mild-to-moderate KOA patients and superior to placebo and corticosteroids treatments (4, 31). Lopes de Jesus et al. (4) assessed in a double-blinded RCT, the efficacy of O2-O3 in 96 patients with symptomatic KOA (Kellgren Lawrence grades II-III) concerning pain reduction and functional improvement compared to placebo (air intraarticular injections). They found that O2-O3 elicited a significant reduction in pain intensity and joint function when compared with placebo after 8 weeks of treatment, providing further evidence for its use as a treatment for KOA. Babaei-Ghazani et al. (31) conducted a RCT study to compare the clinical outcome among 62 patients with KOA (Kallgren-Lawrence grades I, II and III) receiving ultrasound-guided injection of steroid vs O2-O3 at 3 months follow-up. They found that both steroid and O2-O3 injections are effective in patients with KOA. Moreover, steroid injection yields an earlier improvement in symptoms of KOA, whereas, the benefits of O2-O3 injection are persistent and last longer.

Others studies found that the efficacy of O2-O3 intraarticular injections for KOA is equal to other

intraarticular injections such as dextrose and HA (29,30). Hashemi et al. (29) in a RCT, compared the effects of prolotherapy with hypertonic dextrose and prolotherapy with O2-O3 on pain and function in 80 patients with mild to moderate KOA (Kellgren-Lawrence grade I and II). They found that 3 months after the treatment there was no statistically significant difference in pain and WOMAC scores between the two groups. Raeissadat et al. (30) conducted a double-blind RCT to discuss the efficacy and safety of O2-O3 intra-articular injection in 141 patients with mild to moderate KOA, compared to HA at 6 months followup. They observed that improvement in all outcome measures was similar between both O2-O3 and HA at 6-month follow-up, hence both can be effectively used for improving function and reducing pain in selected KOA patients.

Finally, the combination of intra-articular O2-O3 therapy with other therapies can provide more positive effects compared to single therapies. Feng et al. (32) in a RCT showed that intra-articular injection of O2-O3 plus oral celecoxib and glucosamine could significantly decrease pain intensity in patients with mild to moderate KOA, and improve their functional status early than oral celecoxib and glucosamine only. Dernek et al. (33) evaluated the difference in efficacy between pain and functional status of 80 patients diagnosed with KOA (Kellgren-Lawrence grade I or II), who received PRP treatment alone compared to PRP treatment in combination with O2-O3 at 6 months followup. They found that although similar efficacy was observed between both treatments, patients receiving PRP treatment in combination with O2-O3 experienced less post injection pain and recovered faster when compared to patients receiving PRP treatment alone.

Other Musculoskeletal Disorders

O2-O3 therapy has been proved to be effective in many other musculoskeletal disorders such as: meniscal injuries (10), sacroiliitis (11), plantar fasciitis (PF) (9, 34) and carpal tunnel syndrome (CTS) (12, 35). Wang et al. (10) compared the clinical therapeutic effects between O2-O3 and triamcinolone acetone

for the treatment of mild meniscal injury in 119 patients. Patients were subdivided in three groups: triamcinolone acetonide (A) group, O2-O3 (B) group and combination of O2-O3 and triamcinolone acetonide (C) group. They found that compared with that before treatment, the total scale of knee joint function improved after treatment in every group and the total scale of group C was better than that of the other groups after the treatment. Moreover, the effective rate of these drugs on joint effusion was 68.18% in group A, 62.5% in group B and 87.18% in group C and the effect of co-injection on joint effusion in group C was significantly better than that of triamcinolone acetonide or O2-O3 alone. They concluded that O2-O3 and triamcinolone acetonide are effective in the treatment of mild meniscal injury, which can relieve symptoms and promote the recovery of joint function and compared with the single injection, the combination of O2-O3 and triamcinolone acetonide is better. Carli et al. (11) reported a case report of a 39-year-old man who complained of LBP and morning stiffness, irresponsive to NSAIDs with a plain radiography and MRI consistent with bilateral grade 1 sacroiliitis who was treated with major O2-O3 autohemotherapy performed 3 times a week for 2 months. They observed that at the end of therapy VAS and BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) decreased to 1.0 and 1.4, respectively. They concluded that O2-O3 therapy seems to be a minimally invasive, effective and promising method in the treatment of sacroiliitis. Babaei-Ghazani et al. (9) performed a RCT to investigate the effectiveness of local O2-O3 injection in comparison with steroid injection in the treatment of chronic PF. They observed that both treatments were effective in reducing pain, improving functional status, and decreasing plantar fascia thickness. Moreover, at 2 weeks, they observed better improvement with corticosteroid injection, while at 12 weeks, the improvement was more significant with O2-O3 injection. Bahrami et al. (35) performed a RCT to evaluate the efficacy and safety of local O2-O3 injection in the management of mild to moderate CTS in two parallel groups. Both of them used the resting volar wrist splint for 8 weeks, while the intervention group received a single dose of local

O2-O3 injection. They found that the combined treatment, was effective in improving signs and symptoms of CTS in mild to moderate cases and significantly more successful in comparison to splinting alone.

Complications

O2-O3 has proven to be safe, with rare adverse effects. The overall procedural complications rate is estimated around 0.1% (15): anterior spinal cord syndrome and acute myocardial infarction caused by paradoxical air embolism in one patient with large patent foramen ovale (PFO) (36), cardiopulmonary arrest (8), vertebrobasilar stroke (37), acute bilateral vitreo-retinal hemorrhages caused by an abrupt transient spike in cerebrospinal fluid pressure (CFP) after disk infiltration transmitted directly through the optic nerve sheaths to the retinal venous circulation, thus causing distension and rupture of peripapillary and retinal capillaries (38), spondylodiscitis (39), fulminating septicemia secondary to disseminated infection by *E. Coli* from the paraspinal muscle abscess that was probably related to a lack of sterility and iatrogenic inoculation of the bacteria during the administration of therapy (40) acute extensive spinal epidural abscess (41), septic arthritis (42), severe headache caused by O2-O3 that was directed to the subarachnoid space because of accidental dural puncture which acted like air and resulted in pneumocephalus (43), transient cortical blindness as a result of bilateral occipito-parietal lobe ischemia caused by paradoxical air embolism in a patient with a large PFO and atrial septal aneurysm (44), few temporary episodes of impaired bilateral sensitivity (13) and paresthesia along the anterolateral compartment of the left leg and hypesthesia over the dorsum of the left foot that is probably related to ventral and dorsal root injury caused by an abrupt transient spike in CFP after disk infiltration (45).

Conclusions

O2-O3 has been proved to be effective in reducing pain in many musculoskeletal disorders with rare

adverse effects if judiciously used according to precisely defined guidelines using a precise ozone generator and collecting a precise gas volume with a defined ozone concentration and an optimal dose for achieving a therapeutic effect without any toxicity.

Conflict of Interest

The author declares that he has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article

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