Oxygen-ozone therapy in musculoskeletal disorders: a narrative review

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ABSTRACT

Oxygen-ozone (O_2O_3) therapy is a spreading intervention proposed to reduce pain intensity and improve physical function in patients with musculoskeletal conditions. The biological effects of O_2O_3 are strictly related to its biochemical properties. It induces moderate oxidative stress and promotes the activation of specific transcriptional pathways related to endogenous radical scavengers. In this context, O_2O_3 therapy promotes immune modulation and inflammatory regulation that might potentially have a key role in the management of patients with musculoskeletal disorders. Interestingly, in recent years a growing number of studies have been showing promising results of O_2O_3 local therapy in different conditions, including low back pain, neck pain, knee osteoarthritis, and temporomandibular disorders. Due to its positive effects in terms of not only pain management but also functional improvement, it has been suggested that this promising therapy might be effectively integrated into a comprehensive rehabilitation approach to musculoskeletal disorders. Despite these considerations, several questions remain open about the effects of O_2O_3 combined with other conventional approaches. The aim of this narrative review was therefore to summarize the state of the art of O_2O_3 local therapy from a rehabilitation perspective, underlining its potential synergisms with other techniques in a multitarget rehabilitation approach to musculoskeletal disorders.

KEYWORDS

Oxygen ozone, oxygen-ozone therapy, ozone, pain management, rehabilitation, musculoskeletal disorders.

Introduction

Ozone (O_3) is an allotropic inorganic molecule discovered in 1839 by Christian Friedrich Schönbein [1]. It is composed of three atoms of oxygen and can be artificially produced from diatomic oxygen (O_2) by specific generators [2,3].

Over the past century, oxygen-ozone (O_2O_3) mixtures have been applied in several settings showing a high safety profile and benefits in several medical fields [3,4]. Despite the positive effects, this technique has some contraindications (including glucose-6-phosphate dehydrogenase deficiency, pregnancy, uncontrolled hyperthyroidism, and severe cardiovascular diseases) and adverse effects (vagal crisis, pain, hematoma in the injection site, and local infections) [3].

However, the mechanisms underpinning the positive clinical effects of O_2O_3 might be found in its biochemical properties targeting blood and human tissues [5]. As a result, it is not surprising that O_2O_3 mixtures have been used in several clinical situations, including wound healing, infections, ischemic disorders, and chronic inflammatory diseases [3,4,6,7]. In this context, bactericidal and virucidal properties and multilevel interaction with inflammatory pathways are the key mechanisms involved in its therapeutic effects. However, several molecular effects have been proposed and several questions are still open in this field.

In rehabilitation settings, local administration of a medical O_2O_3 mixture is a key option to treat chronic conditions and musculoskeletal disorders characterized by significant impairment of physical functioning and quality of life [3,4]. In this scenario, O_2O_3 therapy might be proposed as part of a comprehensive rehabilitation approach in order to optimize functional recovery and improve pain management during physical therapies through a mini-invasive approach. Different administration modalities have been proposed including local (transdermal, subcutaneous, intramuscular, intradiscal, and intracavitary) and systemic (blood administration/ozonated autohemotherapy) ones [3].

Despite these considerations, there remain several concerns about the integration of this technique in routine clinical settings and the therapeutic effects of O_2O_3 therapy combined with rehabilitation have not been characterized in depth. On the other hand, it should be noted that historically O_2O_3 therapy has been considered an oxidant stressor and that clinical use of this technique combined with different approaches has been

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introduced only in recent years. Thus, it is not surprising that large-scale studies exploring the integration of O_2O_3 into the multidimensional management of patients with musculoskeletal disorders are still lacking.

Therefore, the present narrative review aims to provide an overview of the scientific literature on the role of O_2O_3 local therapy in patients affected by musculoskeletal disorders focusing on the potential synergisms with physical therapies and the benefits in terms of pain management.

Biological effects

The macroscopic effects of O_2O_3 therapy might be related to a wide variety of biochemical reactions induced in human tissues [7]. In particular, O_3 is characterized by a powerful oxidizing activity, reacting in the human environment with water and polyunsaturated fatty acids (PUFA) [5].

The O_2O_3 mixture reacts with water, producing H_2O_2, a reactive oxygen species (ROS) considered one of the main O_3 messengers in human body. In addition, superoxide ion (O_2^-) and hydroxyl radical (OH-) are other reactive products having a role in oxidative stress induced by O_3 [2,8]. On the other hand, 4-hydroxynonenal (4-HNE) is produced from omega-6 PUFA and 4-HHE (trans-4 hydroxy-2-hexenal) is produced from omega-3 PUFA [3].

In human tissues, these oxidative molecules were shown to be effectively targeted by endogenous radical scavengers, including glutathione peroxidase, catalase, superoxide dismutase, and NADPH quinone-oxidoreductase [8-10]. Interestingly, it has been proposed that the rapid and limited oxidative stress might induce the rapid degeneration of endogenous radical scavengers, promoting the activation of transcriptional factors [6,10]. In this particular pathway, nuclear factor-erythroid 2-related factor 2 (Nrf2) plays a key role, migrating into the nucleus and binding the Maf protein to promote the transcription of antioxidant response elements [6].

As a result, it has been proposed that Nrf2 might have different interactions with NF-ϰB, a widely known key regulator of inflammatory processes [11]. Moreover, O_2O_3 mixture might affect prostaglandin synthesis, and secretion of leukocytes and macrophages, with intriguing implications for inflammation and pain transduction [12].

Altogether, these findings underline that several biological processes are involved in the therapeutic effects of O_2O_3 therapy. In this context, a precision medicine approach targeting the specific biological processes involved in the pathogenesis of musculoskeletal conditions might be used to elucidate the role of O_2O_3 therapy in a comprehensive rehabilitation approach to musculoskeletal disorders, thus paving the way for personalized management.

Oxygen-ozone therapy in musculoskeletal disorders

O_2O_3 therapy has shown promising features in terms of musculoskeletal pain management, as confirmed by several studies [9,13-16]. In this setting, optimal pain management is one of the main goals of rehabilitation, the aim being to improve physical functioning and physical performance, which can often be impaired in painful musculoskeletal conditions. On the other hand, inflammatory processes and nociceptive perception are the key targets of O_2O_3 therapy, the latter interacting with both inflammation pathways and pain modulation through the moderate oxidative stress induced by the reaction of O_3 with biological tissues [9,13-16].

As a result, several musculoskeletal conditions might benefit from O_2O_3 therapy, and several studies are currently available in this field [3,4,6,7]. In particular, the role O_2O_3 therapy has been studied in depth in patients affected by low back pain (LBP), neck pain, knee osteoarthritis (KOA), and temporomandibular disorders (TMD) [3,4,6,7].

Low back pain

LBP is a highly prevalent disorder affecting a growing number of people worldwide and leading to increased disability related to impaired physical functioning and psychosocial implications [17]. Although the optimal therapeutic approach is based mainly on the specific pathophysiology of LBP [18-21], several therapeutic approaches have been proposed in the complex management of this debilitating condition. It has also been proposed that a multitarget intervention might be effective in chronic LBP not only to optimize pain management but also to minimize complications related to pharmacological pain management, including gastrointestinal adverse events (nausea, vomiting, constipation), cardiovascular side effects (hypertension, bleeding), and risk of falling [22,23].

In this context, O_2O_3 therapy has been supported by growing literature on LBP related to disc herniation, showing positive effects, reducing pain intensity and improving physical functioning of patients with LBP [24,25]. Accordingly, recent reports underline the positive effects of O_2O_3 therapy in other common spinal degenerative diseases, including spondylarthrosis, disc protrusion, sequelae of vertebral fractures, and failed back surgery syndrome [24,26-28]. Nevertheless, a proper etiological diagnosis of LBP is mandatory in order to tailor the optimal therapeutic approach, especially as other musculoskeletal conditions show a similar clinical presentation (e.g., lumbar facet syndrome, piriformis syndrome, trochanteric bursitis, sacroiliac joint pain) [3,7]; however, to date, the level of evidence to support the efficacy of O_2O_3 therapy in the management of these conditions remains low.

Interestingly, to manage LBP, the literature reports different administration modalities. In particular, O_2O_3 might be administered using a minimally invasive approach, targeting paravertebral muscles corresponding to the metamer of the herniated disc [24,26]. Other proposed approaches for managing LBP are intradiscal or intraforaminal O_3 applications under fluoroscopy or tomographic guidance, with positive effects in terms of pain relief reported in the literature [29,31]. On the other hand, the fact that intradiscal or intraforaminal O_3 applications need imaging guidance severely limits the feasibility of these interventions; however, recent research supports a role for ultrasound in guiding procedures in LBP with intriguing implications for a precision approach to paravertebral O_2O_3 administration [32].

Overall, O_2O_3 therapy might be considered an effective and safe therapeutic intervention that could potentially be integrated into the comprehensive management of LBP. Further studies are needed to better characterize the optimal administration modalities in specific LBP etiologies and the role of specific treatment protocols in the comprehensive rehabilitation management of LBP.

Neck pain

Chronic neck pain is a debilitating disorder leading to significant disability and health care costs [33]. It has been estimated that approximately 10% to 20% of the population report neck pain, and in the United States the condition is second only to LBP in terms of annual workers' compensation costs [34,35].

Rehabilitation is a cornerstone of the therapeutic approach to neck pain, with several reports supporting its effects in symptom management and in improving physical functioning [36,37]. On the other hand, O_2O_3 therapy is commonly used in clinical practice as a complementary therapy in the management of neck pain related to cervical spondylolysis or osteoarthritis and intervertebral disc degeneration [3]. However, there is still little evidence supporting its therapeutic effects, and few studies are currently available in this field. Raeissadat *et al*. [15] compared O_2O_3 therapy with lidocaine injection into the trapezius trigger points and dry needling, reporting significant improvements in terms of pain intensity but without significant differences between groups. Similarly, Lin *et al*. [38], assessing the effects of ultrasound-guided O_2O_3 cervical injections in patients with neck pain due to zoster infections, reported significant effects in terms of pain intensity.

Although positive results are reported in the current literature, the low number of studies available in this field, combined with their low-quality design, severely limits the strength of the recommendation supporting O_2O_3 therapy in cervical pain management [15,38]. Therefore, good quality studies are needed to characterize the possible role of O_2O_3 in the comprehensive rehabilitation management of neck pain, the synergisms with other rehabilitation techniques, and the potential advantages of multitarget management of this burdensome disabling condition.

Knee osteoarthritis

KOA is a disabling condition clinically associated with joint pain and periarticular muscle weakness, and leading to progressive functional impairment and reduced independence in activities of daily living [39]. In this context, too, rehabilitation is a cornerstone of non-surgical treatments proposed to reduce symptoms and improve physical functioning and might be effectively integrated into the pharmacological management of this debilitating condition [40].

Noninvasive procedures have been shown to be a suitable option in patients not responding to conventional therapies, with growing body of literature now focusing on corticosteroid injections, hyaluronic acid (HA) injections, platelet-rich plasma injections, and mesenchymal cell injections [40-42].

On the other hand, O_2O_3 administration in patients with KOA is an underestimated procedure supported by several reports in the current literature [13,43-45]. A recent systematic review with meta-analysis reported significant improvements in terms of knee pain intensity, stiffness, and function after intra-articular O_2O_3 administration [45]. In addition, Feng *et al*., in a recent study [44], assessed the effects of intra-articular administration of O_2O_3 versus conventional therapy (anti-inflammatory drugs combined with glucosamine), reporting significant advantages in terms of pain reduction in the intra-articular O_2O_3 therapy group.

In addition, it is interesting to note that O_2O_3 might be combined in specific protocols with HA, with a recent report underlining better results of O_2O_3combined with HA compared with O_2O_3 or HA alone [43]. Despite these considerations, some concerns have been raised over the long-term effects of intra-articular administration of OO_2O_3 [13]. Thus, this promising technique might potentially be considered in the context of an integrated rehabilitation program for patients with KOA to optimize long-term outcomes.

Taken together, these findings suggest that intra-articular administration of O_2O_3 should be taken into consideration in the non-surgical management of patients with KOA. However, further good-quality studies are necessary in order to understand the role of these treatments in a comprehensive rehabilitation approach.

Temporomandibular disorders

TMD are musculoskeletal conditions characterized by pain and limited range of motion of the jaw. They may have both intra- and extra-articular features [46]. Several rehabilitation approaches have been proposed in the symptom management of TMD, including manual therapy, laser therapy, transcutaneous electrical nerve stimulation, dry needling, occlusal splint devices, and behavioral therapies [47-49]. Interestingly, it was recently proposed that O_2O_3 therapy might have a role in counteracting inflammation in TMD, due to the multilevel influence of O_2O_3 therapy in regulating inflammatory cascades [4].

Celakil *et al*. [50], in a recent randomized controlled trial, assessed the effects of O_2O_3 therapy in masticatory muscle pain compared with placebo. The authors reported a significant decrease in pain intensity after the treatment, suggesting that O_3 might be considered an effective therapy for reducing TMD symptoms.

On the other hand, the recent systematic review with meta-analysis by Torres-Rosas *et al*. [51] showed positive results of O_2O_3 therapy in terms of pain intensity and physical function expressed as maximal mouth opening. However, no significant advantages were reported compared with other treatments, including occlusal splint or pharmacotherapy.

Taken together, these findings suggested that O_2O_3 therapy should be considered as a complementary treatment in the management of patients with TMD, with positive effects in terms of symptom management and physical functioning improvement. Thus, it should be considered in integrated rehabilitation management of these disabling conditions.

Tendinopathies

Tendinopathies are musculoskeletal conditions characterized by pain, swelling, and functional impairment [52]. The non-surgical approach is the first-line intervention in the management of patients with tendinopathies; quite varied therapeutic inter-

ventions have been proposed, and to date there is no consensus about the optimal management of different tendinopathies. O_2O_3 therapy has been proposed to have a role in this field [53].

Ulusoy *et al*. [9] recently assessed the effects of O_2O_3 administration in lateral epicondylitis compared with corticosteroid injections. Interestingly, the authors reported similar short-term results in both groups; however, O_2O_3 therapy showed significant advantages after 9 months.

Similar results were reported by Atar *et al*. [54] in patients with rotator cuff tendinopathy. In particular, the authors reported lower short-term benefits of O_2O_3 administration compared with corticosteroid injection, while positive advantages in terms of pain intensity and physical function were shown after 12 weeks [54].

However, few reports supporting the effects of O_2O_3 therapy in different tendinopathies are available in the current literature, and clear indications on evidence-based protocols are far from being fully characterized. Moreover, the proper management of patients with tendinopathies should be based on a precise diagnosis and the optimal therapeutic approach should include comprehensive rehabilitation based on both the patient's characteristics and the pathophysiology of the disease. Having said this, O_2O_3 is a safe and complementary option that might be considered in the comprehensive management of patients with tendinopathies.

Contraindications and side effects

Although the current literature reports several positive effects of O_2O_3 local applications for the treatment of musculoskeletal disorders, this technique is not free from contraindications and potential adverse events. Because of the intrinsic oxidative stress mediated by O_2O_3 administration, the main contraindication to O_2O_3 therapy is glucose-6-phosphate dehydrogenase deficiency. Other contraindications include pregnancy, uncontrolled hyperthyroidism, heart failure, and severe cardiovascular diseases. Moreover, potential adverse effects, which might be mainly related to improper administration procedures, are reported in the literature. These include vagal crisis, pain, hematoma in the injection site, and local infections [3].

Conclusions

This narrative review provides a broad overview of O_2O_3 therapy local applications in musculoskeletal conditions, underlining the functional implications of proper pain management with this mini-invasive approach. Despite these considerations, there remain several open challenges in characterizing the role of O_2O_3 therapy in multimodal therapeutic interventions. Moreover, the role of O_2O_3 combined with other treatments is still far from being fully characterized.

On the other hand, the evidence summarized in this review highlights that O_2O_3 therapy might be considered a safe and promising intervention in patients suffering from painful musculoskeletal disorders, improving physical function and patient quality of life.

However, further studies are needed to better characterize the optimal administration modalities and doses of O_2O_3 in different conditions, in order to optimize tailored rehabilitation interventions in patients with musculoskeletal disorders.

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