Ultrasonography for oxygen-ozone therapy in musculoskeletal diseases

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Abstract

Over the years, infiltrative oxygen-ozone therapy has shown clinical benefits in several musculoskeletal disorders, due to its potential analgesic, anti-inflammatory, antioxidant and immunomodulatory effect. Ultrasonography is a safe, non-invasive imaging, easily available, and has the additional advantage of being real time for imaging and image-guided procedures of the musculoskeletal system. This review explains the numerous promising ways in which ultrasonography can be useful in oxygen-ozone therapeutic practices for musculoskeletal disorders, in order to improve safety and accuracy of treatment.

Key words: ozone; ultrasound; oxygen-ozone therapy; musculoskeletal diseases; ultrasonography; paravertebral injection; peritendinous zone; intraarticular ozone

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INTRODUCTION

Oxygen-ozone therapy

The oxygen-ozone (O₂–O₃) therapy is based on the application of a mixture of 5% O₂ and 95% of medical O₃. O₃ is a colorless natural gas with a characteristic odor; it is composed of three oxygen atoms. Its high reactivity gives it a short half-life (in gaseous form at 20°C, its half-life is 3 days, while in liquid form, its half-life is 20 minutes). This means that it cannot be stored but must be produced just before use. It can be produced artificially by subjecting diatomic oxygen to a high-voltage electrical discharge, through the endothermic reaction 3O₂ → 2O₃. In literature,¹-⁵ the followings are widely described, what O₃ is, how it acts, how its toxicity can be controlled, the route of administration, the behaviour and fate of the O₃ messengers (reactive oxygen species, and lipid oxidative products) after coming into contact with body fluids, and the therapeutic effects of O₃. Probable mechanism of action of the O₂–O₃ mixture may be found in the biochemical properties of O₃, including an antalgic, anti-inflammatory, antioxidant effects and an immunomodulatory action.⁶ These are performed by: (i) activating the cellular metabolism, (ii) reducing proinflammatory prostaglandins synthesis or the release of allogenic compounds, (iii) increasing release of immunosuppressor cytokines, (iv) reducing oxidative stress through induction of the synthesis of antioxidant enzymes (superoxide dismutase, glutathione peroxidase, and catalase) and, in addition, (v) amelioration of the tissue O₂ supply through hemoreologic action, vasodilatation, and angiogenesis stimulation.⁶ ⁷ This effects are the basis of O₃ clinical effectiveness.

In particular, the therapeutic efficacy of O₂–O₃ therapy is due to the controlled and moderate oxidative stress produced by the reactions of O₃ with several biological components. Calculated and transitory O₃-induced oxidative stress generates a number of second messengers in various intracellular signaling pathways. These are capable to induce an antioxidant response through activation of nuclear transcriptional factors and upregulation of the antioxidant enzymes. O₃ acts as a hormetic prodrug,⁸ on the basis of phenomenon that says “the exposure of an organism to a low level of an agent, harmful at high levels, induces an adaptive and beneficial response”.⁹ Effectiveness and toxicity of O₃ depend on the intensity of the oxidative stress. At the appropriate dose, O₃ paradoxically upregulates the antioxidant defences and is capable of reversing a chronic oxidative stress.¹⁰

O₂–O₃ therapy is widely used in the field of musculoskeletal disorders, mainly to the treatment of vertebral column diseases (intervertebral disc protrusion or herniation, failed back surgery syndrome), osteoarthritis (degenerative or inflammatory), and several other joint-tendinitis affections.⁶ ¹⁰ O₂–O₃ mixture has different routes of administration. In spinal disorder an indirect technique can be used by injecting the gas into the points localizable in the paravertebral muscle corrisponding to the metamer of the herniated disc. This approach can be defined as the indirect approach. Alternatively a intradiscal injection of ozone at the level of the pathologic intersomatic space under radioscopic control can be performed. This approach can be defined as the direct approach. In osteoarthritis O₂–O₃ mixture is administered via intra-articular and periarticular injections. In tendinopathies O₂–O₃ mixture is administered via peritendinous injections.¹¹ The contraindications to the use of O₂–O₃ therapy are some patient conditions such as pregnancy, glucose-6-phosphate dehydrogenase deficiency (favinism), uncontrolled hyperthyroidism, severe cardiovascular diseases and heart failure.¹¹ The adverse effects of O₂–O₃ therapy can be distinguished from those of the O₂–O₃ mixture and the administration technique. The feeling of heaviness or burning at the injection site is first documented until a vagal crisis. The side effects based on the technique of administration are: hematoma due to injury to blood vessels, pain, and
local infection due to a non-sterile procedure. However, these events are rare and can be avoided with good procedures.12

Ultrasonography
Musculoskeletal ultrasound is a non-invasive, rapid, safe, relatively inexpensive imaging modality, emits no ionizing radiation, and can be performed in the outpatient clinical setting.13 It is capable of providing real-time dynamic tissue assessment,14 allowing exploration of the musculoskeletal system, and it is ideally suited for image-guided interventions. The basis of image-guided intervention is the ability to identify the region to be injected (target), confirm placement of the needle at the appropriate location thereby minimizing risks of injury to adjacent structures,15 and ensure correct localization of therapeutic agent. Recently, an increasing number of physicians have integrated musculoskeletal ultrasound into their clinical practices to ensure patient care.16 This review provides a brief overview of the potential use of ultrasonography in the treatment of musculoskeletal diseases with O2–O3, in order to facilitate the performance of safe and precise interventions.

ULTRASONOGRAPHY AS A PRE-PROCEDURE ASSESSMENT BEFORE THE PARAVERTEBRAL INFILTRATION
Intramuscular paravertebral injection of O2–O3 mixture is a technique used frequently in clinical practice to treat spinal diseases. It has been also defined as “chemical acupuncture” because both the needle and gas injection have a role in eliciting a complex series of chemical and neurological reactions leading to the disappearance of pain in the majority (positive responses in 70–80% of cases) of patients with low spinal pain.17 The intramuscular injection is administered in the paravertebral muscles corresponding to the metamer of each vertebral segment affected. For each treatment session, one or several (up to four) symmetrical injections of 5–10 mL of O2–O3 gaseous mixture (15–20 µg/mL concentration) for site were performed, via an extraspinal lateral approach.17 Currently, needles are available in a wide range of lengths and gauges: for paravertebral injections gauge (from G22 to G25 in lumbar region, and G25 to G30 in cervical region) and length changes according to the patient body size. Under sterile conditions, medical O2–O3 mixture is injected at a distance of 2 cm laterally from spinous processes in the paravertebral muscles, making sure not to be inside a blood vessel. The gaseous mixture should be introduced very slowly in order to avoid pain and promote homogeneous distribution of the gas through the muscle fibers.18 Usually, the O2–O3 infiltrations are performed using an aseptic free-hand approach after the injection site with O2–O3 mixture was identified caudally from L4. In the cervical region, the spinous process of C7 (vertebra prominens) can be easily recognized at palpation. Other anatomical landmarks are the inferior tip of the mastoid process, situated just superiorly and laterally to the transverses processes of C1 and the superior border of the thyroid cartilage corresponds to C4.21

Ultrasoundography can be used to integrate the landmark-guided approach to improve accuracy and safety of the treatment. Ultrasonography allows a detailed pre-procedural examination of the area of interest, identifying and characterizing the various anatomical structures of the cervical and lumbar spine. An ultrasound examination of the spine can be performed combining a sagittal and a transverse scan with ultrasound to identify and mark the intervertebral level, while a transverse scan to evaluate the paravertebral muscles, injection site with O2–O3 mixture. In the paramedian oblique sagittal scan, the probe is placed approximately 2 cm lateral to the midline in the sagittal axis and it is tilted softly medially toward the midline. In this view, the sacrum is identified as a flat hyperechoic structure with a large acoustic shadow anteriorly. Sliding the transducer in a cranial direction, the gap between the line of the sacrum and the lamina of the L5 vertebra (with its typical sonographic “sawtooth” appearance) represents the L5–S1 interlaminar space (Figure 1).

The successive lumbar interlaminar spaces, corresponding to the intervertebral spaces (from L5/S1 to L1/L2), can be determined by counting upward from the lumbosacral junction. To improve the accuracy of ultrasound to identify the intervertebral space can combine a counting-up approach from the L5–S1 junction with a “counting-down” approach from T12, identified by its articulation with the twelfth rib.22 This combined approach is helpful in patients with anomalies of the lumbosacral junction as sacralization of the L5 vertebra, or less commonly, lumbarization of the S1 vertebra, which occurs approximately in 12% of the general population.23 By placing...
each interlaminar space in the centre of the ultrasound screen, its position can be marked on the skin at the midpoint of the long axis of the probe. This prevents misidentification of the level during later scanning in the transverse plane.

Once the examination in the parasagittal oblique scan is completed, the transducer is rotated 90° into a transverse orientation and is positioned with the centre of the probe over the spinous process (transverse spinous process view). In this view, the tip of the spinous process is visible as a superficial hyperechoic line with vertical linear acoustic shadowing beneath, while at either side of the base of the spinous process the laminae appear as bright white horizontal landmarks. Lateral to the spinous process and upon the laminae the erector spinae muscle can be visualized (Figure 2).

For cervical spine examination a median sagittal scan and a transverse scan are performed. In the median sagittal scan, the transducer is applied over the midline to obtain a long axis view of the spine. In this view, the C1 vertebra is visualized immediately caudal to the occiput and has a rudimentary spinous process or not, while C2 vertebra shows the first real spinous process (Figure 3). Moving the transducer caudally, the other spinous processes are identified up to C7, known as vertebra prominens.

Once the median sagittal scan and the identification of the correct cervical level has been performed, the transducer is rotated 90° into a transverse orientation and is positioned with the centre of the probe over the spinous process (transverse spinous process view). In this view, the bifid spinous processes of C2–6 vertebra (Figure 4) and the large and unique process at C7 level (vertebra prominens) can be visualized by moving the probe caudally.

Once the cervical or lumbar vertebral level to treat in transversal axis is identified, the transducer is then moved laterally to each side to visualize the left and right paravertebral muscles. These are bordered medially by the spinous process and inferiorly by the vertebral laminae. In this view, in order to evaluate the O₂–O₃ injections site, we suggest performing two linear measurements, at 1.5 cm lateral from the spinous process in cervical region (Figure 5A), and at 2 cm lateral from the spinous process in lumbar region (Figure 5B). The measurements are: (I) the distance between the skin and hyperechoic fascia surrounding the superior border of the muscle, named by authors with the acronym Skin-Muscle Distance; (II) the distance between the skin and hyperechogenic vertebral lamina (used as a landmark to identify the deep border of the muscle), named Skin-Lamina Distance (Figure 5). These two measurements provide useful information about paravertebral muscle depth. The Skin-Muscle Distance allows estimating the minimum depth necessary to achieve the musculature, and it is influenced by the thickness of the subcutaneous tissue. The Skin-Lamina Distance allows an assessment of the maximum paravertebral muscles depth. Based on these measurements
it is possible to identify the needle length range that is most suitable to perform infiltration. Thinner and shorter needles can be used if the aim is to decrease patient discomfort during injections; while longer needles can be used if the goal is release therapeutic agent nearby vertebral lamina. In both cases, the injection can be performed being sure to be inside the musculature. Furthermore, the ultrasound examination is helpful in patients with a peculiar distribution of adipose tissue in which the most commonly needles used for \( \text{O}_2-\text{O}_3 \) injections are not long enough to achieve the paravertebral muscles. In these cases, the Skin-Muscle Distance is decisive for the correct needle choice.

**Ultrasonography as a Real-time Imaging Modality During Injections**

Peritendinous and intra-articular injections require a thorough knowledge of the anatomy and an accurate physical examination to determine the optimal injection site and placement of \( \text{O}_2-\text{O}_3 \) mixture. Given the complexity of the anatomical sites of injection and the proximity to adjacent structures as vessels or nerves, to ensure safe and appropriate placement may be extremely difficult. The use of ultrasound as a real-time imaging modality allows to evaluate the area of interest, reaching the target structure with precision and avoiding damaging important adjacent anatomical structures, confirm placement of the needle at the appropriate location, and ensure correct localization of therapeutic agent. The choice of the ultrasound probe depends on the characteristics of the structure to be sampled. The linear probe (10–15 MHz) provides adequate visualization of most superficial sites; joints, superficial muscles, and superficial bones. To visualize sites located deeper as deep joint articular surfaces, a linear probe with lower frequency or a convex probe (5–10 MHz) may be required. Before any definitive procedural intervention a preliminary scan through the site of interest should be performed, to inspect regional anatomy and visualize nearby neuro-vascular structures. Color or Power Doppler imaging can be used to evaluate region vascularity and help guide the procedure to minimize the potential for bleeding. In the case of peritendinous injections, the muscle and tendon should be scanned throughout their course. Placing the probe in longitudinal section, the needle is best visualized when its long axis is parallel to and in line with the long axis of the probe. In this plane, it is seen as a linear echogenic structure with a path of least resistance, and is visible for a variable time. In this view has been observed a higher success rate for injections.\(^{26}\) In intra-articular injections, the joint space should be scanned in all dimensions to determine the safest and most optimal injection site. The selection of the needle is based on the depth of the structure being injected. The needle is inserted in target structure under direct sonographic visualization and it should be visible at all times during the procedure (Figure 6A). The \( \text{O}_2-\text{O}_3 \) injection, performed under ultrasound-guide, allows visualizing the real-time diffusion of the gas in the appropriate location (joint space or peritendinous soft tissues) and prevents inadvertent application into the tendons or peri-articular structures. The \( \text{O}_2-\text{O}_3 \) mixture appears as hyperechoic area in the peritendinous soft tissue with a well-defined shadow, or most rarely, with a faint shadow (Figure 6B).

The ultrasound-guided procedure, as demonstrated in literature for other therapeutic agent injection, reduces pain both during and after the injection, decreases overall patient discomfort, and improves joint or muscle mobility more than traditional blind injections.\(^{25-28}\) Obviously, it requires good experience and deep knowledge of the anatomy.

**Ultrasonography as Post-procedure Valuation of the Oxygen-Ozone Distribution in the Tissue**

Once injected in the site to treat, ultrasonography may be useful tool to evaluate the \( \text{O}_2-\text{O}_3 \) mixture distribution in the tissue. \( \text{O}_2-\text{O}_3 \) mixture spreads in the tissue following the path of least resistance, and is visible for a variable time. In intramuscular paravertebral injection, ultrasonography shows a homogeneous gas distribution through the paravertebral muscle fibers (Figure 7); in peritendinous injection, \( \text{O}_2-\text{O}_3 \) mixture spreads along the peritendinous soft tissue (Figure 8).

**Conclusion**

Ultrasonography, used as a pre-procedure assessment before the paravertebral infiltration, is useful to identify the needle length range most suitable to perform infiltration. Ultras-
nography, used as a real-time imaging modality (or guide) during peritendinous and intra-articular injections, is useful to provide patients with safe and accurate treatments, following in real time every step of the procedure. Moreover, used as post-procedure valuation, ultrasonography allows confirming the optimal distribution of the \( \text{O}_2-\text{O}_3 \) mixture injected in the tissue. In according to this review ultrasonography may be an added value to improve procedural accuracy, maximize patient’s safety, and optimize clinical outcomes.

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Study design, concept and definition: EL, ERC, AM, SMN, FS, DT, MV, MCV. All authors read and approved the final version of the paper for publication.

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