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Mechanism of Action of Oxygen Ozone Therapy in the Treatment of Disc Herniation and Low Back Pain

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Abstract In the low back syndrome the pain has a multifactorial origin and ozone can surprisingly display a number of beneficial effects ranging from the inhibition of inflammation, correction of ischemia and venous stasis, and finally inducing a reflex therapy effect by stimulating anti-nociceptor analgesic mechanisms. The intradiscal and intramuscular injection of oxygen–ozone is a successful approach comparable to other minimally invasive procedures, but the elucidation of the mechanisms of action remains elusive. This communication shortly reports the mechanisms of action of oxygen ozone therapy at the level of intervertebral disc and paravertebral muscles.

Keywords Low-back pain syndrome • Oxygen ozone injection • Mechanism of Action of Ozone Therapy

Introduction

Despite a large number of biochemical studies, the use of ozone in medicine still remains controversial. At present, ozone therapy is most commonly associated with the treatment of disc herniation and/or low back pain throughout the injection of an oxygen–ozone mixture in the vertebral disc or in the paravertebral muscles.

In the case of disc herniation, the clinical effects of ozone are reported to be related to the lysis and reduction of disc, and the success of the therapy is based on the possibility of statistically estimating in neuroradiological studies the reduction or disappearance of the anatomic protrusion.

Nevertheless, confusion persists concerning the amount of gas mixture, the concentration of ozone, the frequency of the therapy and the site of injection. The same efficacy has been reported with different methodologies such as paravertebral, intradiscal, intraforaminal or epidural ozone injections, and the variability of clinical responsiveness of patients in different studies with the same technical approach introduces further difficulties in the standardisation of the therapy.

Controlled and randomized clinical trials are urgently needed to prove the validity of ozone therapy.

This article briefly reports the biochemical mechanism of action of ozone in the field of neurosurgical disease.

Intradiscal Injection

In the case of gas injection directly into the nucleus pulposus, we have some evidence that ozone dissolves in the intradiscal water and reacts with the complex macromolecular components such as proteoglycans and glicosoaminoglycans. The reaction entails an oxidation of these substrates (galactose, glycuronic acid, glycine, 4-hydroxyprolin) and the breakdown of intra- and intermolecular chains leading to disintegration of the three-dimensional structure. Its collapse frees the entrapped water that, after reabsorption, allows a decrease of intradiscal pressure and possibly a disappearance of pain due to the reduced pressure on the nervous root. However, since ozone is very often released also along the injection path (i.e., intraforaminal) the final therapeutic effect is due to the combination of vasculomediated and biochemical effects (improved oxygenation, correction of local acidosis, disappearance of venous and lymphatic stasis). It seems important to postulate that in the intraforaminal space, the presence of lipids, an excellent substrate for ozone, may favour the release of oxidized phospholipids to be included among LOPs: surprisingly, during inflammation, these compounds can inhibit inflammation as it has been shown in mice undergoing a lethal endotoxic shock. Thus, ozone appears to display paradoxical and unexpected useful

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effects such as inhibition of the release or inactivation of proteinases and likely enhancement of the release of immunosuppressive cytokines such as TGFβ or/and IL-10. Even more surprising is the recent evidence suggesting that ozone, by inhibiting COX-2, blocks the synthesis of proinflammatory prostaglandin E_2. Another important analgesic effect may be derived by the induction of antioxidant enzymes resulting in the adaptation to chronic oxidative stress. These novel and surprising aspects have allowed formulating the concept of the ozone-paradox.

Paravertebral Injection

The indirect approach consisting of the injection of 10–20 ml of gas in one to four sites of the paravertebral muscles in patients with back-ache, has become very popular in Italy, China, and Spain. This procedure is named "chemical acupuncture" because both the needle and oxygen–ozone must have a role in eliciting a complex series of chemical and neurological reactions, leading to the disappearance of pain in the majority (70–80% of good response) of patients with low back-pain. It has been clearly established that the ozone concentration must be neither below 18–20 mcg/ml, nor higher than 25–28 mcg/ml. If it is too low, it is hardly effective but higher than 20 mcg/ml can be, especially during the initial treatments, too painful and may even cause lipothymia and a risky vasovagal reflex. On the other hand, it has been often observed that, after five to seven treatments, the pain threshold raises and therefore we can carefully increase the ozone concentration.

What happens to ozone injected into the paravertebral muscle? Ozone dissolves mostly into the interstitial water and reacts immediately with antioxidants and PUFA generating hydrogen peroxide and LOPs, as it has been amply described. These compounds stimulate local C-nociceptors and cause a transitory but usually tolerable pain that is an essential requirement for achieving the final therapeutic effect.

Moreover, another overlooked effect is caused by the mechanical factor induced by injecting oxygen that is about 98% of the gas volume. This certainly is another stimulus causing a feeling of tension and pressure on the muscle and it is, at least in part, responsible of the final therapeutic effect. Unfortunately, in spite of several formal requests, only once the effect of oxygen alone was systematically ascertained when, unintentionally, it was injected into the lumbar muscles of 30 patients against 66 experimental (ozone: 20 mcg/ml). Interestingly, albeit slightly less even control patients improved. All other reported studies have NO CONTROL and this, from a scientific point of view, is a pitfall. This serious drawback has been recently emphasized by an American scientist, who has specified that the FDA will not approve the use of ozone unless a randomized and controlled study is performed. A sham injection with normal saline has been proposed, but this is not correct and should be substituted by the injection of oxygen that represents the bulk of the gas mixture.

The stimulation of nociceptors is able to elicit the elevation of pain threshold and an antalgic response via the well-known descending antinociceptive system. As it occurs during a cutaneous stimulation, or acupuncture, albeit at a far lower level, the introduction of the needle, reinforced by the pressure of the gas plus the generated chemicals, induces a sort of prolonged stunning of nociceptors. It is known that an algic stimulation of the skin and muscles can reduce pain through the mechanism of diffuse noxious inhibitory control (DNIC). Recently it has been shown that even minimal acupuncture that is the superficial needling of NON-acupuncture points, has a similar benefit as real acupuncture on patients with tension-type headache. Thus, although it is known that the placebo effect is important, it is important to ascertain its relevance.

Conclusion

In conclusion, the probable mechanisms playing a role are as follows:

(a) Activation of the descending antinociceptive system.
(b) Release of endorphins blocks transmission of the noxious signal to the thalamus and cortex.
(c) Hypostimulation (elevation of the activation threshold) linked to the oxidative degeneration of C-nociceptors.
(d) Simultaneous psychogenic stimulation of the central analgesic system induced by the gas injection, somehow due to a placebo effect.
(e) The localized oxygenation and analgesia are most important because they permit muscle relaxation and vasodilation, thus a reactivation of the muscle metabolism, by favouring oxidation of lactate, neutralization of acidosis, enhanced synthesis of ATP, Ca^{2+} reuptake and edema reabsorption.

In conclusion, we have seen that pain has a multifactorial origin and that ozone can surprisingly display a number of beneficial effects ranging from the inhibition of inflammation, correction of ischemia and venous stasis and finally inducing a reflex therapy effect by stimulating anti-nociceptor analgesic mechanisms.

The intradiscal and intramuscular injection of oxygen–ozone is a successful approach comparable to other minimally invasive procedures but a standardization of procedure and controlled randomized studies are needed.

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Conflicts of Interest Statement I declare that I have no conflict of interest.

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