Review Article

The Use of Ozone in Medicine

Emma Borrelli[1]* and Velio Bocci[2]

[1]*Department of Medical Biotechnologies, University of Siena, Italy;* [2]*Emeritus Professor of Physiology, University of Siena, Italy*

Corresponding author:
Emma Borrelli,
Department of Medical Biotechnologies,
University of Siena, Italy,
Tel: 0577586760;
E-mail: emma.borrelli@unisi.it

Abstract

The use of ozone became a normal practice after the initial studies by Dr. H. H. Wolff (1979) in Germany. Today, in this Nation, is used by over 12.000 physicians but only after Bocci's study it is used very proficiently either in chronic inflammatory diseases or in orthopedics. It has been shown to be very effective and absolutely atoxic when used in dosages which induce only a well-tolerated oxidative stress either for autohaemotherapy or in orthopedics. It will be described what ozone is, how it can be proficiently used, what are its messengers, what will be their effects and what are the therapeutic effect.

Keywords: Ozone; Oxygen; Medicine

Introduction

The use of ozone in medicine: State of the art

Ozone is made by three oxygen atoms (O_3) and its molecular weight is of 48.000. Ozone has a cyclical structure with a distance among oxygen atoms of 1.26 A and exists in several mesmeric status in dynamic equilibrium. Its solubility (ml) in 100 ml water at 0°C of either ozone or oxygen is 49.0 ml or 4.89 (ten folds lower), respectively. Consequently the great solubility of ozone in water allows its immediate reaction with any soluble compounds and biomolecules present in biological fluids. Among oxidant agents, ozone is the third strongest, after fluorine and persulphate, a fact that explain its high reactivity. [1]

Ozone is formed from pure oxygen via an endothermic process allowed by a very high voltage gradients set up between the electrodes of the Siemens's tube:

$3O_2$ ----$2O_3$ ---- 68.400 cal

This reaction is reversible and consequently ozone is hardly storable. A normal medical ozone generator produce ozone concentrations equivalent from 1 up to 100 mcg/ml but for medical purposes ozone concentrations from 10 up to 40 micrograms/ml is used. Indeed ozone is carefully collected with a glass syringe in dosages ranging from 10 up to 40 µg/ml. [2] Ozone measured in terms of micrograms/ml is used with great care either for the auto haemotherapy or for direct use in case of orthopedics. In all cases low dosages of ozone are used either because it is only necessary to induce the minimal oxidative stress which is sufficient to induce a medically useful response.

The use of ozone in systemic diseases (Ozonated blood)

This is feasible because the therapeutic ozone dosage is mixed with the patient blood ex vivo. It is important to mention that human blood (both plasma and cells) contains a great number of antioxidants including hydrosoluble ones such as uric acid, ascorbic acid, cysteine, glutathione, albumin, some chelating proteins such as albumin (CYS 34) and enzymes such as catalase, GSH redox system, NADPH and superoxide dismutases (SOD). The relevance of the antioxidants in plasma is enormous and it allows performing ozone therapy. In 100 ml of human blood it is possible to measure about 5 mg/dl of uric acid, 1.5 mg/dl ascorbic acid, albumin containing cysteine 34 and eleven nucleophilic groups. Thus the variety of extracellular and intracellular antioxidants is able to explain how bland amounts of ozone can be perfectly tamed with the results of stimulating the biological system without deleterious effects. A large number of experimental studies reported that the antioxidant reservoir decreases no more than 30% in relation to ozone doses between 10 and 40 mcg/ml of ozone per ml of blood. Moreover this partial depletion is corrected in about 20 minutes ex vivo thanks to the recycling of dehydroascorbic acid, GSSG, vitamin E radical, NAD (P) radical. Indeed the potent antioxidant reservoir of blood decreases no more than 35% after ozonation and fully recovers in about 20 min ex vivo. Thus a first conclusion is that we can perform safely ozone therapy because a small ozone dose is fully controlled by the potent antioxidant system of blood. Consequently we measure rapid antioxidant regeneration because we have demonstrated the manteinance of a normal antioxidant system. [3]

Literature Review

Which are the pathologies more suitable to be treated with a success?

All chronic inflammations develop in conjunction with a chronic oxidative stress. This means that protection of reactive oxygen and mitogen species (ROS/RNS) is very much increased while the production of necrotizing antioxidants is very much depressed. Diseases with this problem are the majority and include all vascular diseases such as those in

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the CNS either preceding a stroke or a chronic limb ischemia, heart insufficiency, age - related macular degeneration (dry form), Chronic obstructive pulmonary disease, likely multiple sclerosis, Parkinson's and Alzheimer's disease. [4,5] Thus a mild ozonetherapy (twice weekly) performed with a progressive slow increase of ozone (first week: 10 µg/ml ozone, ranging from 100 to 150 ml in relation to body weight; 2nd week:15 µg/ml of blood; 3rd week: 20 µg/ml of blood; 4th week: 25 µg/ml of blood; 5th week: 30 µg/ml of blood; 6th week: 35 µg ozone per ml of blood). With this scheme in most cases the patient reports a feeling of wellness but if he/she reports to be tired and sleepy, we must reduce the ozone dose. However about 85% of patients report a feeling of wellbeing and increased energy. After six months therapy, one ozonetherapy is enough and, by the tenth month, the patient reduces the symptomatology and improves the performance status. At this purpose it is possible to speculate that the beneficial effects on chronic degenerative diseases, especially on chronic vascular diseases, are also obtained throughout the increase of nitric oxide (NO) production in microcirculation. During the reinfusion of ozonated blood in patient, the vast expanse of the endothelial cells is activated by albumin-LOP, resulting in an increased production of NO, plasma S-nitrosothiols and S- nitrosohemoglobin. While NO has an half-life of less than 1 sec, protein- bound NO can exert vasodilatation also at distant ischemic vascular sites with relevant therapeutic effects. [6]

Why ozonetherapy is very effective in this particular set of diseases?

There are multiple reasons: the first consists in having evaluated a weak oxidative stress. The very small amounts of ozone reacts immediately in the glass bottle and, when the so-called ozonated blood is infused in the donor, ozone is no longer present. While oxygen slowly oxygenates all the erythrocytes, ozone reacts immediately with antioxidants present in the plasma and with polyunsaturated fatty acids (PUFA). Consequently the antioxidants decrease by 10-30% (and they will be later rapidly reduced) while PUFA undergo peroxidation. H_2O_2 and aldehydes are very important because H_2O_2 can penetrate all blood cells. The erythrocytes will shift the hemoglobin curve to the right and this process will facilitate the oxygenation of ischemic tissues. In blood leukocytes, ozone is able to activate the NFkB which allows a transitory increase of synthesis of TNF alpha, IFN gamma, IL-2 and IL-8. The long term effects of ozone therapy from immunological point of view is a mild and controlled production of cytokines because the activated leukocytes home in lymphoid microenvironments and contribute to enhance the immune system. [7] The two final alchenals, mostly represented by hydroxyl-nonenal (4-HNE) will be partly eliminated by the liver and kidneys but mostly will bind to either the Cys 34 of albumin or to GSH or cysteine. These molecules, via the circulation, will easily transfer 4-HNE into the cytoplasm of many cells. The cells contain in cytoplasma an inactive transcription factor called nuclear transcription factor NrF2 bound to a larger inactive factor with several exposed-SH groups called Keap 1 rich in cysteins. When 4-HNE binds to Cys 273 or Cys 288 of Keap-1 causes the release of the important molecule NrF_2. This molecule (weight about 90.000) is now free to move into the cell nucleus and this step either prevents of replaces the exacerbations of stress induced disease typical of cardiovascular diseases, COPD, age-related macular degeneration and probably malaria as well. The NrF2 (90-11 m.w.) after binding to a small MAF protein, activates the antioxidant response element (ARE) able to activate some 230 genes belonging to the phase II antioxidants and detoxification response. The induced genes include the most important synthesis of GSH, of various GSH enzymes, NADPH, NAD (p)-quinone-oxidoreductase 1 (NQO1), UD Psyalil-transferase and heme-oxygenase-1 capable of increasing the level of CO and bilirubin. NrF_2 also inhibits insulin and growth hormone production,thus increasing stress resistance. In the next experimental studies we will also analyse a possible induction of Sirtuin 1 gene after major ozonated autohemotherapy because, similarly with mild exercise and caloric restriction, it is possible to speculate that systemic ozone therapy can induce Sirtuin-1, an anti-aging gene. [8] Ozonetherapy is very cheap and, if performed twice weekly, it is well accepted mostly because, within 3-4 weeks, the patient reported to be rejuvenated. [9]

The use of ozone in orthopaedic diseases

The pathophysiology of these diseases is complex, often characterized by the distruction of the articular cartilage with increased matrix degradation due to the release of proteoglycanases. Moreover collagenase-activated chondrocytes and monocytes can release IL-1, TNF-alpha and prostaglandins which amplify the inflammation. [10]

It is surprising that after an initial pain, small doses of ozone induce great relief for a long time. Two different approaches have been proposed: the simpler of the two is the indirect approach or chemical acupuncute because the 5-10 ml of oxygen ozone (about 20%) injection is performed into the paravertebral muscle corresponding to the site of pain. This procedure has become very popular in the world but the ozonetherapist must be warned to avoid an excessive dose of ozone, which may induce a complex and dangerous neurovegetative over-reaction. The approach consists in one or two injections of 5-10 ml gas to be done about 2 cm bilaterally to the spinosus process at the level of the pain. Results are: as about 40% optimal, 35% marked improvement and 15-20% minimal or no results. The mechanism of action is due to the hig solubility of ozone in the muscle interstitial fluid. It is expected to suddently generate some H_2O_2 and lipoperoxides able to stimulate amyelinic fiber (nociceptors) able to elicit an antalgic response via the descending antinociceptive systems. The injection must be performed very carefully and slowly for avoiding lipothymia. The mechanism of action is probably due to:

- Activation of the descending antinociceptive system;
- Elevation of the activation threshold linked to the oxidative degeneration of C-nociceptors;
- Release of endorphins able to block the transmission of the noxious signal to the thalamus and cortex;

- Simultaneous psychogenic stimulation of the central analgesic system induced by the gas injection(s). The localized oxygenation and analgesia are important because they permit muscle relaxation and vasodilation, thus a reactivation of muscle metabolism.

Discussion

When the paravertebral injection of ozone does not work (in about 25-30% of patients), the direct approach or intradiscal injection of oxygen –ozone may solve the problem. The direct intradiscal injection of O_2-O_3 must be carried out under radioscopic control: the needle is inserted in the center of the pathologic intersomatic space just before the direct insufflations of 3-15 ml of the gas mixture. The ozone concentration ranges between 20-30 mcg/ml. Usually up to 70% of patients have shown a great outcome. The most likely mechanism follows: ozone dissolves in the discal nucleus pulposus and generates both H_2O_2 and OH which are very reactive. Indeed they dissolve proteoglycans and collagen type I and II which are components of the degenerate nucleus pulposus leading to its breakdown. Thus the reabsorpion of hydrolytic products and water lead to progressive shrinkage and disappearance of the herniated material. The reduced mechanical irritation decreases the sensitivity of the nerve axons and also the inflammation disappears. This means that ozone rapidly blocks inflammatory reactants and stimulates the restitutioadintegrum. Probably the release of TGF beta-1 and bFGF favour the reorganization of the residual nucleus pulposus with incipient fibrosis. Release of endorphins with activation of the antinociceptive system and an elicitation of a placebo effect are very likely. A positive response may reach the level of 80% success. Side effects are very rare. [11]

In conclusion today it appears that very small amounts of ozone surprisingly are able to solve a painful and invalidating problem. These results, due to very small dosages of ozone, ought to stimulate an intelligent reflection of the most stubborn opponents of the use of the ozone in medicine.

Conclusion

In this brief review we have analyzed the many “pros” and the very rare “con” capable of using O_2-O_3 either in parenteral or localized therapies. It remains surprising that health authorities do not help to improve the situation and remain entangled in political problems.

Conflict of Interest

All authors disclose that there was no conflict of interest.

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