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Review

Reliable and effective oxygen-ozone therapy at a crossroads with ozonated saline infusion and ozone rectal insufflation

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Abstract

Objectives This review aims to highlight the advantages and safety of oxygen-ozone therapy (OOT) and to suggest ways to enhance its acceptance.

Key findings The treatment of a herniated disk by injecting a gaseous oxygen-ozone mixture inside the nucleus pulposus is a great clinical success. However, the use of OOT lags for a number of reasons, including lack of standardization, the need for numerous treatments, lack of knowledge and even denial. Anecdotally, several million treatments by OOT have been performed worldwide indicating its usefulness, mainly in peripheral arterial diseases and age-related macular degeneration. The scepticism that accompanies the systemic use of ozone can only be overcome by demonstrating the validity of OOT in controlled and randomized clinical trials. Cheaper and quicker methods, such as ozonating physiological saline with successive infusion as well as ozone rectal insufflations, are becoming popular, however, such alternative procedures are erratic, unstable and liable to be toxic, with deleterious consequences, and are likely to discredit the beneficial use of ozone.

Summary The approval of ozone in terms of both therapeutic efficacy and safety will depend on the results achieved by authoritative clinical trials.

Introduction

During the last decade, oxygen-ozone therapy (OOT) has slowly come of age and today it is used in many countries. This has come about as scientific studies have clarified the mechanism of action of ozone when it comes in contact with human blood and biological fluids. With the exception of pathologies such as decompression sickness, CO and smoke poisoning, severe blood-loss anaemia and gas gangrene, where hyperbaric oxygen therapy is extremely useful, OOT appears to be more beneficial than hyperbaric oxygen therapy in peripheral arterial diseases complicated by chronic ulcers,[1] osteoradionecrosis, refractory osteomyelitis[2] and necrotizing fasciitis.[3] OOT originated in Germany in around 1970 but for many years was performed in an empirical fashion without knowing how ozone acted.[4] As ozone is one of the most reactive oxidants ($E^\circ = +2.076V$), it seemed difficult to understand how it could be therapeutically useful. However, in recent years, the concepts of paradoxical pharmacology,[5] hormesis[6] and systems biology[7] have become accepted. The ozone paradox has been clarified and all the elicited biochemical reactions and pharmacokinetics of the generated compounds appear well within the realms of standard biochemistry, molecular biology and pharmacology.[8,9] Indeed, among alternative approaches, OOT is well qualified to be accepted as a conventional medicine.

In Russia, Ukraine and Cuba, treatment with ozone is already a reality in public hospitals, but they have adopted doubtful administration modalities such as the infusion of ozonated saline or oxygen-ozone rectal insufflations of excessive amounts of gaseous ozone. These surrogates have been developed because they are inexpensive, rapid and applicable to thousands of patients every day. Owing to the uncertainty in both concentration and stability of crucial compounds, no regulatory agency will accept these procedures and this discredits OOT. The aims of this review were: (1) to pharmacologically evaluate both reliable and doubtful methods of ozone administration; (2) to establish precise rules for performing this therapeutic treatment; and (3) to briefly summarize the state-of-the-art medical use of ozone.

Reliable and Doubtful Methods of Ozone Administration

Classical oxygen-ozone therapy

OOT has two forms: major-OOT (M-OOT), involving 50–200 ml of human blood, and minor-OOT (m-OOT), involving about 5 ml of blood. In both cases, blood is treated with precise ozone dosages and then the ozonated blood is either intravenously infused back (M-OOT) or intramuscularly injected into the donor (m-OOT). M-OOT has the scope of modifying the biological response especially to restore and enhance the antioxidant capacity of patients affected by inflammatory and age-associated disease states including typical vascular diseases (stroke, chronic heart disease and peripheral arterial diseases),[10] the dry form of macular degeneration,[4] and insulin-resistant linked type 2 diabetes.[11] The m-OOT is intended as an unspecific protein therapy causing physiological immune stimulation in patients with recurring viral infections such as herpes type I and II.[4] Ozone should be generated only when necessary and no storage is possible. For this reason, ozone generators that are safe, reliable and reproducible are crucial. Ozone formation can mainly be achieved by corona discharge generators.[12] An important point to be considered is the use of medical grade oxygen instead of air as the feed gas; in fact, since the latter contains about 78% nitrogen, variable amounts of highly toxic nitric oxide will be produced. When the gas mixture is added to blood (containing 1 ml of sodium citrate 3.8% per 9 ml of blood or, if possible, Ca-heparin, 20 IU/ml) both gases dissolve into the water of plasma but ozone is 10-fold more soluble than oxygen. The PaO_2 raises up to 400 mmHg but the hyperoxygenation is therapeutically negligible. The real drug is ozone which immediately reacts with either hydrosoluble antioxidants present in the plasma (uric acid is oxidized to allantoin, ascorbic acid to dehydroascorbate, glutathione (GSH) to oxidised GSH and methionine to the corresponding sulfoxide) and with polyunsaturated fatty acids bound to albumin to instantaneously give hydrogen peroxide and bioactive aldehydes such as 4-hydroxy-nonenal, 4-hydroxy-hexenal and 4-oxo-2-nonenal, which form an adduct with the Cys34 of albumin or with GSH for Michael addition. On the basis of a recent metabonomic study, the Cys34 of albumin does not appear to be oxidized to sulfenic acid by ozone within the therapeutic range of 15–80 μg/ml ozone per ml of blood.[13] On the other hand, if a trace of anion superoxide is formed, it is also reduced to hydrogen peroxide. Moreover, depending on the ozone dose, other alkenals can react with the imidazole nitrogen of histidine or/and with the amine nitrogen of lysine,[14] because each albumin molecule contains nine nucleophilic groups and represents the most important detoxifying molecule.[15] Alkenals are also rapidly converted into the corresponding alcohols by alcohol dehydrogenase, aldehyde reductase and aldose reductase.[16,17] Moreover, another detoxifying pathway is via glutathionylation by GSH-*S*-transferase A4 which is specific for 4-hydroxy-nonenal.[18] Within the therapeutic range, it has been shown that no lipid peroxidation of the erythrocytic membrane occurs.[19] Potential lipid peroxide formed is rapidly reduced to hydroperoxide via peroxiredoxins and GSH peroxidases. Hence, within less than the canonical 5 min of mixing the blood with the gas phase, ozone has fully reacted and generated no more than 40 μM of H_2O_2 (in the case of an ozone concentration of 80 μg/ml) as typical reactive oxygen species and 1–3 μM of alkenals as typical lipid oxidation products (LOPs). But what is the fate of these two messengers? The H_2O_2 gradient formed between plasma and intracellular H_2O of blood cells is very transient because H_2O_2 easily passes through the cell membrane, but inside the cell its concentration is never greater than 10% of the extracellular one[20,21] because it is quickly reduced to water by the abundant GSH and thioredoxin.[22] Its intracellular half-life is around 10–30 s, and in plasma it is still less than 1 min. Moreover, intracellular H_2O_2 activates the following biochemical pathways in blood cells: (1) owing to a variable increase of 2,3-diphosphoglycerate, the oxyhaemoglobin curve shifts to the right and erythrocytes can deliver more oxygen to hypoxic tissue; (2) activation of nuclear factor-$\kappa\beta$ in lymphocytes results in a mild immune stimulation due to up-regulation of the synthesis of several cytokines; and (3) release of platelet growth factors that appear to be useful for stimulating the healing process. Next, during infusion of ozonated blood, any free alkenal is either detoxified or excreted via bile or urine. Alkenals linked to Cys34 of albumin as adducts or glutathionylated come in contact with billions of endothelial and parenchimal cells with multiple biological effects: (1) enhanced release of NO and nitrosothiols following vasodilation; (2) up-regulation of heme-oxygenase I with release of CO and bilirubin, which displays vessel dilation and antioxidant activity; (3) up-regulation of antioxidant enzymes (superoxide dismutase, GSH peroxidase; GSH reductase; catalase; glucose-6-phosphate dehydrogenase), γ-glutamate cysteine ligase, γ-glutamyl-transferase and phase II enzymes. In-vitro studies have demonstrated that the translocation of NF-E2-related factor 2 into the nucleus activates the expression of antioxidant-responsive element-containing genes.[23,24] Once the infusion of ozonated blood was completed in an age-related macular degeneration patient, the half-life of malonyldialdehyde was 4 min, demonstrating the efficiency of the catabolic system in eliminating aldehydic compounds.[25] Experiments in progress have shown the crucial relevance of alkenals as the inducers of the antioxidant response or, in other words, the role of alkenals as the critical messengers of ozone. The precise sequence and the molecular pathway involved will soon be clarified and this appears to be the last step in scientifically clarifying OOT.

Anecdotally, the value of M-OOT as a biological response modifier has been shown by private physicians with millions of treatments being performed in all parts of the world during the last decade. A few deaths due to the direct intravenous injection of oxygen-ozone gaseous mixture have been recorded and this approach has been prohibited by the International Ozone Association since 1984.[26] Ozone is the initial trigger but when it is used in precisely defined conditions, it generates two classes of messengers (reactive oxygen species and LOPs), which during their short lifetime activate several biochemical pathways without toxic effects. However, the final word will only come with the results of well-controlled, randomized clinical trials in suitable diseases.

Ozonated saline

In 1994 one of us (VB) tried to ozonate simple physiological saline (0.9% NaCl) by adding 250 ml of the oxygen-ozone gas mixture with an ozone concentration of 70 μg/ml (hence an ozone total amount of 17.5 mg) to 250 ml of saline in a glass bottle of 500 ml. After 2–3 min mixing, the ozonated saline was ready. When it was intravenously infused in the arm, it procured an initial phlebitis which receded after about 36 h. It was found that ozone induced a progressive formation of hydrogen peroxide and chemiluminescent effects, suggesting the generation of free radicals, possibly superoxide radical, singlet oxygen and residual ozone.[27] Noxious agents such as H_2O_2 and a transitory formation of NaClO can easily irritate the endothelium. Moreover, the Fenton's reaction may occur because the saline solution may contain a trace of Fe^{2+}, leading to the formation of hydroxyl radical, and subsequently of transient NaClO formation.[28] The different ozone reactivity and disappearance both in the absence and in the presence of chloride ions are shown in Figure 1. In detail, the diagram reveals the increase of O_3 bubbled at 70 μg/ml concentration (gas inflow 1.5 l/min) and the following decrease in 400 ml of either ultrapure water or physiological saline when ozone bubbling was stopped after 25 min. The absorbance values were measured every 2 min at $\lambda = 260$ nm. As expected, at an O_3 concentration of 10 μg/ml, the curves were very similar, even if absorbance values were considerably lower (unpublished data). In fact, apart from the actual reaction pathways of chloride ions in physiological saline (0.9% NaCl) by ozone, hypothetical hypochlorite as well as its oxidised species such as chlorate could be very irritating and noxious compounds, even at a concentration below the instrumental sensitivity limit. From 1995, in Russia, physicians started to use ozonated saline in hospitals in all patients, claiming that ozonated saline was clinically as effective as M-OOT. However, the saline was ozonated by bubbling an oxygen-ozone gas mixture with a very low ozone concentration (1–3 μg/ml) for 20 min. Supposedly, in Russia there are too many patients as well as insufficient facilities to perform the M-OOT. To the best of our knowledge, a comparative analysis of the therapeutic efficacy between ozonated saline and M-OOT has never appeared in an international peer-reviewed scientific journal. The apparent lack of toxicity by using such a low concentration is reasonable because, at the infusion time, which is usually more or less delayed from preparation, 250 ml of ozonated saline may contain only 0.5 mg of residual ozone and H_2O_2 at a very low concentration (1–2 μM). Consequently, during the infusion these compounds will be readily neutralized by the wealth of antioxidants present in the circulating blood. Whether biochemical effects due to residual H_2O_2 and ozone will occur remains uncertain. The difference between these two procedures are summarized in Table 1. As the infusion of ozonated saline is very cheap, less time-consuming than M-OOT and quite remunerative for unscrupulous practitioners, physicians have also started to use it in some Western countries and it is likely that it will be extensively used in poor countries, possibly at a dangerous higher O_3 concentration. Indeed, Ikonomidis *et al*. have

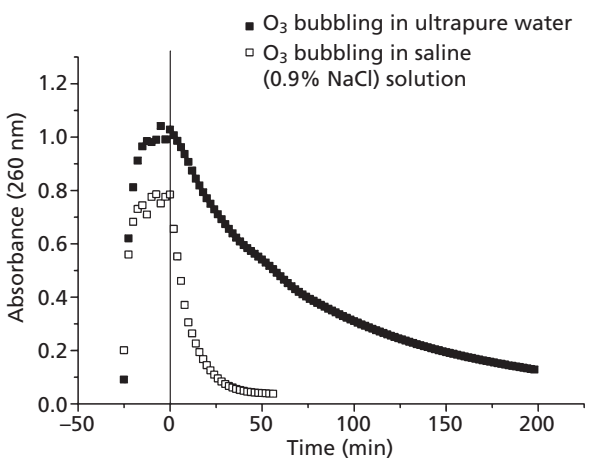

Figure 1 Ozone solubility and disappearance profile both in the absence and in the presence of 0.9% sodium chloride.

Table 1 Conceptual and practical differences between major oxygen-ozone therapy and ozonated physiological saline

	M-OOT	OS
Volume	150–200 ml[a]	~250–500 ml[b]
Reaction sites	*Ex vivo*, in the glass container	*In vivo*
Biochemical effects	Reactive oxygen species, *ex vivo* alkenals, *ex vivo* and *in vivo*	*In vivo*
Average ozone dose	4–16 mg	0.75–1.5 mg

M-OOT, major oxygen-ozone therapy; OS, ozonated physiological saline. [a]Usual ex-vivo blood volumes with Na-citrate or heparin in an ozone-resistant glass bottle. [b]The volume variability depends upon gender, flow rate and venous blood flow (the higher the flow, the lower the biochemical effect).

reported that they maintain the saline solution under a constant flow of O_3 during intravenous infusion but they warned that the maximum amount of O_3 daily administered is usually 4–5 mg and should never exceed 8–10 mg.[29] In their publication they stated that 'if we exceed these rates, the over coagulation syndrome starts' and they strongly recommend that coagulation tests be performed before starting therapy. These warnings reinforce our preliminary objection to this approach. Moreover Foksinski *et al*. detected 8-oxodeoxyguanosine, typical oxidative DNA damage in lymphocytes of atherosclerotic patients after the infusion of ozonated saline, which is a worrying result never detected after M-OOT.[30] It is clear that ozonation of saline is an unstable process because, if it is not promptly infused, O_3 totally decomposes in 60 min and therefore this preparation does not comply with the pharmacotherapeutic principle that requires stability and an exact knowledge of the constituents. Another problem is that commercial ozone generators differ and they often have a variable gas output (from 1 up to 3–5 l/min) and consequently the total amount of O_3 delivered can vary from 1- to 5-fold. Therefore some ozonetherapists, in the absence of a suitable preparation, may risk intoxicating the patient. Another disturbing factor is that blood flow in the cubital vein varies especially in women, with the consequence of an uncertain blood/H_2O_2-O_3 relationship, implying variable biooxidation. Thus, a growing use of ozonated saline, although less dangerous than the direct intravenous infusion of O_2-O_3 that some practitioners of naturopathy still perform, does not represent an improvement and in any case it will be never accepted by the FDA or by EU health authorities.

Ozone rectal insufflation

Another route of administration of O_3 is the insufflation of an O_2-O_3 gaseous mixture into the rectum. In 1936, when Aubourg proposed the procedure,[31] it appeared a reasonable application for treating chronic colitis and fistulae. Nowadays, it has been proposed to 'treat' many other diseases.[32–40] The insufflation of a volume of 200–250 ml of gas into the rectum/colon at an O_3 concentration ranging from 5 to no more than 35 μg/ml can be precisely done, but the effective O_3 dose is unpredictable because of possible flatulence and the presence of a more or less abundant luminal content. Thus, it is clear that a significant fraction of the dose will be neutralized by faecal material. The residual O_3 dose will dissolve and be neutralized into the layer composed of glycocalix and mucoproteins covering the mucosa. O_3 instantly and fully reacts with these compounds, but only a fraction of LOPs will be absorbed by the mucosa and the H_2O_2 will be totally reduced. Moreover, in a recent study with rabbits, ozone colorectal applications induced changes in erythrocytes aggregation and fragility, but the real therapeutic effect on vascular diseases, diabetes and cancer remains uncertain.[40] Once again, while in Western countries many patients object to this route, in Cuba there are thousands of patients treated every day, and this rapid, inexpensive procedure has always adopted the administration of 200 ml O_2-O_3 mixture with an O_3 concentration of 50 μg/ml (O_3 dose: 10 mg).[32] However, the O_3 concentration appears to be too high and during prolonged use may be mutagenic. As this route is so uncertain it should not be used in controlled clinical trials.

Acceptance by Orthodox Medicine: Some Impediments

The clinical use of ozone presents a number of controversies that can be summarized as follows. (1) The deplorable past use of ozone such as direct gaseous intravenous injections, now prohibited, and/or the use of unreliable ozone generators, now replaced by the latest generation which by photometric determination in real time allows measurement of the precise ozone concentration, the gas volume output, and hence the dose. The correct range of therapeutically useful ozone concentrations has been accurately determined and varies between 10 and 80 μg/ml (0.21–1.68 mM) of ozone per ml of blood. The axiom 'start low, go slow' represents the best criterion, suggesting that treatment begin with 20 μg/ml of ozone per ml of blood, slowly scaling up to 60–70 μg/ml throughout 15–20 sessions, which is suitable to induce an antioxidative response in any patient, as a sort of ozone tolerance. A metabonomic study did not show any change in the blood profile after treatment with oxygen or with 80 μg/ml of ozone per ml of blood.[19] (2) It is unfortunate that ozone therapy is also used by unscrupulous and incompetent physicians who, besides using ozonated saline, mix ozone therapy with other complementary treatments. Moreover, the reliable photometric system, indispensable for the measurement of precise ozone concentrations, costs about €4000 and only a percentage of generators on the market have it. (3) The lack of sponsors and funds means that controlled and randomized clinical trials cannot be undertaken, which is a major obstacle. Thus, only small trials have been performed thanks to the goodwill of a few clinicians. Consequently, the application of ozone therapy in all public hospitals is still being delayed by prejudice, lack of knowledge, competition with pharmaceuticals and the disinterest of the health authorities such as the FDA in the USA and the EMA in Europe. However, in Russia, Ukraine and China many patients are treated with simplified, yet uncertain, ozone therapy methods. In the 'Madrid Declaration on Ozone Therapy', as approved by the International Scientific Committee of Ozonetherapy, a list of the therapeutic uses of ozone has been published.[41] Obviously, the performance of appropriate clinical studies in the most relevant diseases showing the validity and lack of side-effects of ozone therapy is urgently needed.

Current State-of-the-Art

Results achieved in clinical trials

The most suitable pathology to be treated by ozone therapy is vascular disease. Most of the attention has been focused on peripheral obstructive arterial disease. A study performed between 1974 and 1980 in 152 patients showed the beneficial effects of M-OOT in comparison with pentoxyfilline and prostanoids, without adverse effects.[42] Also, Mattassi *et al*.[43] ($n = 68$) and Romero Valdés *et al*.[44] ($n = 60$) found an improvement in at least 44% and 35% of patients, respectively. Other trials (most of them in less than 20 patients),[45–50] although showing a beneficial effect over established therapy, were performed with different ozone concentrations and schedules. The most recent trial was carried out in 28 patients randomized to receive either their own ozonated blood or a cycle of prostacyclin infusion.[1] All the patients continued conventional treatments with statins, antihypertensive and antiplatelet aggregation drugs. Ozone therapy proved to be more effective and far less expensive than the prostanoid analogue in terms of pain reduction and improvement of quality of life, but treatment was carried out for only 7 weeks (14 treatments).

In general, it appears that the usual OOT performed for at least 4 months (32–48 treatments) and maintained thereafter with four treatments each month is considered the best treatment for peripheral obstructive arterial disease. Despite frequent venipuncture, patients are mostly compliant because they notice the benefits of the therapy and frequently report a feeling of wellness. On the contrary, an irrational procedure called Celacade, supported by many millions of dollars from Vasogen Inc. (Canada), consisted of exposing 10 ml of human blood to an oxygen/ozone gas mixture (ozone concentration 15.35 g/m^3) delivered into the blood at a flow of 240 ml/min and UV light (253.7 nm) at a temperature of 42.5°C for about 20 min. The treated blood sample was removed from the system and immediately administered by intragluteal injection to the donor patient. Two treatments were given on consecutive days, followed by a third on Day 14. Subsequent treatments were given at 4-week (28 days) intervals for at least 22 weeks, for a total of eight injections. Such a procedure used an expensive device able to deliver an enormously toxic dose of ozone (107.5 mg per ml of blood) plus undetermined UV irradiation at 42.5°C.[51] The final ozone dose is about 15 000-fold higher than the average ozone dose used in classical OOT and the extremely high oxidation of blood causes complete denaturation of blood components.[13] This procedure was designed to establish a non-specific immunomodulation therapy in the hope of reducing the inflammatory process and the chronic oxidative stress present in vascular diseases. It has proved to be useless in two multicenter, randomized, double-blind, placebo-controlled studies (SIMPADICO and ACCLAIM trial) enrolling about 3000 patients with critical vascular pathologies.[52] These trials have proved two things: the excessive dose of ozone is useless and the value of a wealthy sponsor.

So far, stroke and chronic heart failure have not receive attention in spite of the fact that only 15% of patients with stroke can receive thrombolysis with alteplase. Millions of people suffer from ischaemic diseases, which represent the major cause of death worldwide. If orthodox medicine accepts OOT as an adjunct to conventional medication a marked leap forward will become noticeable.

Ozone treatment for the dry form of age-related macular degeneration

Throughout the world there are more than 30 million people searching for a therapy slowing the progress of age-related macular degeneration. However, ophthalmologists can only prescribe antioxidants and zinc, which are only minimally effective. Since 1995, almost 1000 patients with the dry form of age-related macular degeneration have been treated with OOT at the Siena Polyclinic (Italy) and three-quarters have shown an improvement of one to two lines on the visual acuity chart.[4] Moreover, it is relevant that the disease does not progress during OOT. Although it induces a pleiotropic response, the main advantage with OOT is due to an increased delivery of oxygen to the retina, the bodily tissue with the highest oxygen consumption. It is worth noting that OOT is useless, even harmful, in the exudative form of age-related macular degeneration and in multigenic and progressive disorders.

Effects of clinical ozone in diabetes

Both diabetes type I and type II lead to vascular and neurological complications. Several anecdotal results have been reported suggesting a marked improvement in glycaemic control and reduction of oxidative stress. A debate on using OOT in diabetes for delaying complications and improving the quality of life has been proposed.[11]

Use of ozone for herniated disks

The application of gaseous ozone in low-back pain due to a herniated disk has been accepted worldwide. Either the method consisting of a small injection (3–5 ml of an oxygen-ozone gaseous mixture with an ozone concentration of 30–35 μg/ml) directly into the centre of the intersomatic space corresponding to the disk herniation[53] or the indirect method of injecting an oxygen-ozone mixture (5–10 ml at 20 μg/ml ozone concentration, the so-called 'chemical acupuncture') into the paravertebral muscles corresponding to the metamers of the herniated disk have a success rate of 80 and 73%, respectively.[54] More than a million people have already benefited from these procedures.

Use of ozone and ozone derivatives as a topical treatment

The therapeutic efficacy of gaseous ozone and its derivatives for the healing of both cutaneous and mucosal infections remains to be demonstrated in controlled clinical studies. All these ozonated compounds are today used in a very empirical fashion and by private physicians or naturopaths. It is understood that ozone, under various formulations, can display a cleansing effect and act as a potent disinfectant able to practically kill all pathogens present in the skin and mucosal surfaces. Furthermore, the decomposition of ozone, by increasing the availability of oxygen in the ischaemic or inflamed tissues, has the additional advantage of improving local metabolism and the proliferation of tissues, essential for the eventual mucosal or/and cutaneous healing.[55] Moreover, while some studies suggest a promising potential of ozone in dentistry, the clinical evidence for its application is not extensive. There is a need for well designed, double-blind randomised clinical trials with adequate sample size, limited or no loss of follow up, and carefully standardised methods of measurement and analysis in order to justify the routine use of gaseous ozone or ozonated water/compounds as a treatment modality for cutaneous and mucosal infections.[56–60]

Rules for Performing Ozone Therapeutic Treatment

A summary of the ethical and legal issues concerning the therapeutic use of ozone has been published by the International Scientific Committee of Ozonetherapy.[61] Briefly, the major points are: (1) only qualified physicians with a university degree specialization in ozone therapy can perform such therapeutic intervention; (2) OOT or other approaches must be carried out following the updated regulations; (3) only ozone generators with a precise photometer, gas pressure control, pure medical oxygen and unused ozone disposable should be used; and (4) the clinic must have an appropriate system of gas elimination as indicated by the European Commission rules and this should be checked annually by a qualified person.

Conclusions

The chemical, biochemical, molecular and pharmacological parameters characterizing ozone therapy are now known and are within the parameters of orthodox medicine. With some limitations, OOT appears to be the optimal treatment in vascular diseases, age-related macular degeneration and possibly diabetes. However, this must be demonstrated with controlled, randomized clinical trials performed in accordance with the Declaration of Helsinki. This is problematic owing to lack of funds and the apparent disinterest of health authorities. Some recent ozone administration modalities such as ozonated physiological saline and ozone rectal insufflations, although inexpensive and quick to perform, do not comply with the pharmacotechnical criteria of consistency and stability required by international health authorities. Only physicians with a qualified university specialization can perform ozone therapy. With ozone therapy being practised in many countries, it is hoped that this review may be useful in correcting some distortions regarding its use and allow some progress in OOT.

Declarations

Conflict of interest

The Authors declare that they have no conflicts of interest to disclose.

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