Chapter 5
How Is Ozone Administered?

Except for the inhalation route (prohibited by tracheo-bronchial-pulmonary toxicity), many parenteral and topical routes are used to administer ozone without toxic effects and minimal discomfort (Table 5.1).

Table 5.1 Routes of ozone administration

Parenteral	Topical or locoregional
Intravenous (IV)	Nasal[a]
Intra-arterial (IA)[b]	Tubal[a]
Intramuscular (IM)	Auricular
Subcutaneous (SC)	Oral[a]
Intraperitoneal (IPE)	Vaginal
Intrapleural (IPL)	Urethral and intrabladder
Intra-articular (IAT)	
(A) Periarticular	Rectal
(B) Myofascial	
Intradiscal (ID)	Cutaneous
Intraforaminal (IF)	Dental
Intralesional (IL)[c]	

[a]To be performed during 30–60 s apnoea.
[b]It is no longer used for limb ischaemia. Hepatic metastasis could be embolized via the hepatic artery.
[c]Intratumoural or via an intra-abscess fistula.

The gas mixture, composed of no less than 95% oxygen and less than 5% ozone has a slight positive pressure and can be collected either with a calibrated syringe (glass is ideal but impractical and has been substituted with disposable, polypropylene, silicone-coated syringes), or, if a continuous flow of gas is needed, by inserting a stainless steel connection to the exit valve of the ozone generator. **RUBBER TUBINGS CANNOT BE USED** because ozone disintegrates the rubber; but a silicon tubing is ideal.

Although ozone is a potent disinfectant, medical oxygen, O-rings and taps are not sterile and, except for rectal insufflation, ozone, as a dry gas, should be filtered for any other application to avoid any possible infection. We are currently using an antibacterial, ozone-resistant, hydrophobic filter with a porosity of 0.2 μm.

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In the past, owing to several deaths due to lung embolism, **THE DIRECT INTRAVENOUS AND INTRA-ARTERIAL ADMINISTRATION OF THE GAS MIXTURE**, containing variable amounts of ozone, **IS PROHIBITED** since 1984. Although the gas is injected very slowly, it favours the formation of a train of gaseous bubbles, where ozone (more soluble than oxygen) dissolves and reacts with blood, while oxygen reaches the right ventricle and then the pulmonary circulation. It ought to be kept in mind that oxygen solubility at 37°C is only about 0.23 ml per 100 ml of plasmatic water and therefore venous plasma cannot dissolve oxygen quickly enough, leading to the formation of a gas embolus. It is a disgrace that naturalist, practitioners and quacks without any medical qualification continue to perform this practice in Kenya, Canada, Jamaica, India, etc. and propagate this technique in other underdeveloped countries where there is no medical control.

The crazy idea of the direct IV gas administration is that ozone, once dissolved in the plasma, inactivates HIV present as free virus particles, just as ozone is used to purify water flowing in an aqueduct.

This idea is totally wrong on the basis of the following calculation: about 500 ml of gas mixture are injected in about 4 h (2 ml/min) with a total ozone dose of 35 mg (70 mcg/ml × 500 ml = 35,000 mcg). A normal 70 kg man has about 5 L of blood which, at rest, circulate entirely in 1 min. This means that a total blood volume of about 1,200 L circulates in 4 h. The plasma volume is about 3 L but it continuously exchanges components (and antioxidants) with some 12 L of extravascular fluids. This implies that the total ozone dose of 35 mg will finally dissolve and react with an actual water volume near 15 L. In any case, as ozone dissolves and reacts immediately, a final ozone concentration in blood is inexistent and only in theory may range between 0.3 and 3.0 mcg/ml, which is an absolutely ineffective virucidal concentration also because free circulating viruses are protected by antioxidants. Even more important is that THE BULK OF INFECTIVE VIRUSES AND PROVIRUSES IS INTRACELLULAR **and, ironically, remains well protected by the intracellular antioxidant system**. The other argument of charlatans is that the direct IV gas administration procures a good blood oxygenation. A simple calculation demonstrates that this is wrong too because, within 4 h, we inhale some 2,400 L of air and, in any case, oxygen therapy can be performed efficaciously and safely by breathing humidified oxygen for a couple of hours at home or under pressure in a hyperbaric chamber according to a standard procedure.

Because of the small gas volume and the gas fragmentation into the limb capillary bed, IA administration does not involve a risk of embolism, but it has been proven to be of no advantage in comparison to the classical ozonated autohemotherapy or even the rectal insufflation of gas. Therefore it is no longer used because repeated arterial punctures should be avoided also because the intraarterial injection induces a precapillaries contraction. On the other hand the practice of therapeutic (with alcohol and cytotoxic compounds) embolism for hepatic metastasis is now in current use and appears to be relatively useful. On this ground it is then possible to postulate the slow intra-arterial (via hepatic artery) administration of 20–40 ml of gas with an ozone concentration up to 80 mcg/ml. The risk of producing oxygen embolism is minimal because the gas will be dispersed into the sinusoidal and tumor capillaries, **possibly**

with direct ozone cytotoxicity on neoplastic cells and without side effects, as may occur with chemotherapeutic compounds. So far I have tested this procedure in a patient with diffused hepatic metastasis without any adverse effects.

What is today's the state of the art in terms of other parenteral routes?

In the past, particularly quacks have used both the IM and SC ROUTES for the treatment of chronic viral hepatitis and vasculopathies. Dangerous volumes of up to 300 ml of gas were subdivided in different sites using ozone concentrations of 10–15 mcg/ml. An ozone concentration of 20 mcg/ml is very painful. In Italy, during the last two decades, many ozonetherapists have earned their livings by performing SC administration of gas (ozone concentration: 2–4 mcg/ml) for the treatment of lipodistrophy, vulgarly known as cellulite. Unfortunately this treatment has become so popular to be carried out in beauty centres by inexpert beauticians, who dared to inject up to 300 ml of gas in a single session. **Even with the utmost care, these large volumes of gas can easily cause pulmonary embolism**. At least **two young women, treated for this trivial pathology, have been killed in Italy** in March 1998 and December 2002, so that the Ministry of Health has correctly prohibited the use of ozone therapy in all cosmetic and beauty centres and, incorrectly, the use of ozonated AHT in all public hospitals.

Obviously, even if this enormous gas volume containing as much as 99.5% oxygen is fractionated into extensive areas of SC tissue of the lower part of the body, it can converge into a deadly pulmonary or/and brain embolism particularly if the woman, as soon as the treatment has been completed gets up and start to walk away. Indeed these two women did not reach the exit door. It remains unknown if these two women had a pervious *foramen ovale*. Indeed a far minor volume and a rest of half hour with a gentle massage of the injected areas may avoid these tragedies.

The direct IV gas administration and the just described practice have deeply compromised the future of ozonetherapy in Italy and it is disgraceful that so much importance has been given to ozone applications in cosmetic treatments. The future of ozonetherapy, if any, will not certainly come by treating cellulite!

To my knowledge the INTRAPERITONEAL and INTRAPLEURAL ROUTES have been used by Russian physicians by using first ozonated water to wash out purulent material and then insufflating into the cavities 100–300 ml of gas with ozone concentrations from 50 down to 5 mcg/ml depending on the gravity of the infection. Ozone dissolves quickly and, by reacting with exudates, can reduce the infection. Furthermore, by stimulating vasodilation and cell proliferation, can lead to a rapid healing. This treatment does not damage the peritoneum, as we have observed after insufflating up to 300 ml of gas (!) into the rabbit peritoneal cavity testing an ozone concentration of 20 mcg/ml. Neither animal discomfort, nor any damage to the peritoneal lining was noted at autopsy after 24 and 48 h. In my opinion, **these routes deserve to be evaluated in peritoneal carcinomatosis and pleural mesothelioma: it is very regretful that oncologists disregard this approach**: daily insufflations of 2–3 L of gas could be easily performed upgrading ozone concentrations from 5 up to 10–15 mcg/ml on the basis of the patient's reactivity. Ozone, during the first 5–10 min, can be directly cytotoxic to neoplastic cells as chemotherapeutic compounds do, with the advantages of avoiding

chemoresistance, not causing toxic effects, bone marrow depression, mucositis and costing almost nothing. The risk of embolism is practically nil and the advantage of a local, albeit transitory, hyperoxia cannot be neglected. A permanent silicone cannula can easily be inserted permanently in the cavities for daily administration. After all peritoneal dialysis has taught us everything about the great potential of the peritoneal cavity where normally 1–2 L of dialysate are exchanged every 4–6 h for removing catabolites. Ozone can directly kills neoplastic cells, activates resident macrophages and neutrophils, while absorption via the lymphatic system of ozone messengers can furthermore induce cytokines such as TNF alpha, IFN gamma, IL-2 that can activate the immune system to complete the destruction of cancer cells. I feel frustrated because since 2000, I wanted to try this route only to have negative answers from oncologists, who exclusively use chemotherapy because well sponsored by wealthy pharmaceuticals. This is indeed a disgraceful situation because also hospital directors blindly refuse to evaluate the ozone efficacy because they are worried about ozone toxicity. I am glad that a colleague, Dr S. Schulz at the University of Marburg, is very much interested in the peritoneal route (Schulz et al., 2008; Bocci, 2008) and I wish him to find an intelligent oncologist. He, recently, informed me that, after intraperitoneal administration of ozone, he has detected the production of prostacyclin, which may have antitumour efficacy. Moreover preconditioning rats undergoing acute cardiac allograft with intraperitoneal ozone prolongs the survival of the graft (Stadlbauer et al., 2008).

Another interesting possibility, applicable to patients frequently affected with chronic viral hepatitis, while undergoing peritoneal dialysis, is to insufflate oxygen-ozone every day intraperitoneally via the catheter already implanted. With a suitable ozone generator at home, autotherapy could be easily performed by the patient between peritoneal dialysis sessions, perhaps reducing the incidence of occasional peritonitis and the loss of permeability. Insufflated volumes could be of 500–1,000 ml starting with an ozone concentration of 5 mcg/ml and slowly upgrading it to 8–10 mcg/ml, thus allowing the induction of ozone tolerance. Obviously antiviral therapy can be complemented by using peg-interferon-alpha or/and ozonated autohemotherapy and rectal insufflation of gas. Clinical experience has taught me that the combined use of several approaches is more proficient than a single one.

Intra-articular, intradisc and intra-foraminal administration will be discussed in the context of orthopaedic diseases.

TOPICAL APPLICATIONS can be performed with the gas mixture and ozonated water and oil.

Nasal, tubal and oral (gingival, mucosal and tonsillary) affections can be treated with suitable metal or silicone cathethers. If the gas is used, a volume of about 20 ml (ozone concentrations from 5 up to 20 mcg/ml) can be sufficient but the patient, after taking a deep breath, must remain in apnoea for 40–60 s and then expire deeply. Aphthous ulcers in the oral cavity can be treated with intralesional mini-injections of ozone (concentration: 5–10 mcg/ml) followed by daily application of ozonated oil. At the moment it has become fashionable to use a silicon cup tightly enclosing

and exposing a herpetic lesion to ozone for 20–30 s (Section 9.16). The application of ozonated oil in the lesion is far more practical and inexpensive.

Ozone treatment in chronic rectal and vaginal infections (bacterial, viral, fungal and protozoan), resistant to conventional treatments, respond very well to ozonetherapy. After inserting about 10–20 cm of a silicon catheter (lubricated with oil), we can start to wash the cavities with abundant ozonated water for removing purulent secretion. Then, we can insufflate either 50-100 or 300 ml of gas (for vaginal or rectal cavities, respectively) for a few minutes and then, with a syringe, apply 5–20 ml of ozonated oil, being careful to lower the ozone concentration as the infection recedes. Vaginal and rectal pessaries and suppositories of ozonated oil can be applied before the night rest. A similar strategy can be used to treat either urethral or bladder infections keeping in mind to lower ozone concentrations between 3 and 10–15 mcg/ml, respectively.

Cutaneous applications regard all kinds of infections (from soreness to diabetic ulcers, burns, insect and jellyfish stings and burns), accidental and war trauma. The gas can be used but the lesion must be sealed hermetically with various ozone-resistant devices to prevent ozone breathing. With a rigid Teflon cup, a slight vacuum can be achieved which, according to Werkmeister (1995), favours local vasodilation. In such a case, the ozonetherapist need an ozone generator equipped with a suction pump. If a dynamic exposure is not feasible, the static system can be achieved with a large polyethylene bag sealed with a wide adhesive tape, not too tight for avoiding venous stasis. All of these systems must contain water because ozone hardly acts in dry form and must dissolve in water. Recently, various types of ozone-resistant chambers, with or without vacuum and with temperature control have been proposed but, all of these complex gadgets do not really improve the basic treatment of cleaning the wound, by applying twice daily a compress wet with ozonated water for about 20 min and then applying the ozonated oil throughout the night.

No one doubts the potent disinfectant activity of ozone (probably slightly inferior to iodine, which is actually too harsh) in regard to Gram negative and Gram positive bacteria, mycetes, viruses and protozoa. The simple and inexpensive treatment with ozonated water and oil is well tolerated, does not have noxious effects and the healing time is far shorter than with any conventional treatment. The latter advantage is due to a number of concomitant factors such as the disinfection, vasodilation, and oxygenation with normalisation of tissue acidosis and reabsorption of oedema (Bertolotti and Izzo, 2006; Borrelli et al., 2008; Faus Vitoria, 2008).

The theoretical sequence of **wound healing** has been schematically represented to happen in three successive stages (Martin, 1997). The scheme presented in Fig. 5.1 shows three phases: **Phase I indicates the inflammation stage**, normally lasting 2–3 days. The bacterial infection successive to a trauma, diabetes, local ischaemia and possibly antibiotic resistance, can become chronic unless we intervene with ozonetherapy. **Phase II corresponds to the intermediate stage** and normally lasts 2 weeks. The synthesis of extracellular matrix (fibronectin, collagen III/I, hyaluronic acid and chondroitin sulphate) is accompanied by an active proliferation of fibroblasts and keratinocytes. The use of ozonated oil, not only prevents

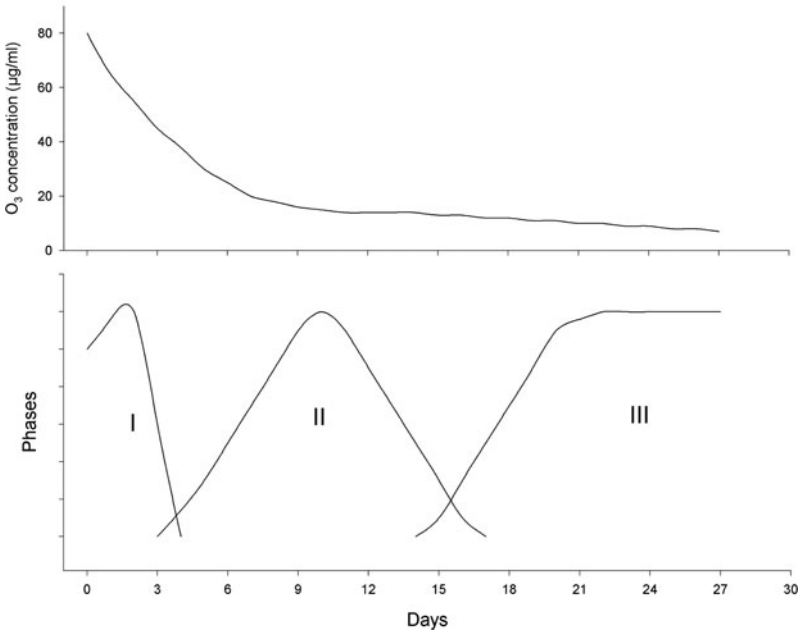

Fig. 5.1 The three phases of wound healing. In the first (I) phase, inflammation prevails, with the presence of neutrophils, macrophages, mastocytes, platelets, bacteria and toxins. Application of ozone inhibits the infection and promotes the second (II) phase, lasting about 2 weeks. During this phase, the constant application of ozone at progressively lower concentrations not only prevents a superinfection but stimulates cell proliferation, the synthesis of fibronectin, collagen III/I, hyaluronic acid and chondroitin sulphate. Macrophages are still present but there is an active proliferation of fibroblasts and keratinocytes. The restitutio ad integrum, i.e. complete reconstruction of the wound, occurs during the last (III) phase. However, excessive release of TGFβ1 may stimulate excessive fibrogenesis with cheloid formation. The above diagram shows the approximate ozone concentrations that must be progressively lowered to avoid inhibition of healing

a superinfection, but stimulates the initial tissue reconstruction. **The restitutio ad integrum, i.e. phase III, includes the final healing and scar tissue remodelling** and may take a long time in elderly and/or diabetic patients. In some cases, excessive release of Transforming Growth Factor (TGF beta 1) may stimulate excessive fibrogenesis with cheloid formation.

In my experience, the successful and fairly rapid healing of a necrotic ulcer in arteriopathic, diabetic and immunosuppressed patients can be achieved by **combining** the parenteral treatment (ozonated autohemotherapy) with the appropriate application of progressively lower ozone concentration of ozonated water and oil. A tight control of glycemia and the combination of these therapies appear to act synergistically. The topical use of antibiotics and growth factors is very expensive and often ineffective.

5.1 Conclusions

The reader will be amazed by the variety of routes of ozone administration. In spite of its intrinsic toxicity, if it is used at judicious doses, ozone is a versatile drug, which can be surprisingly useful in several diseases. Even local infections or neoplasms at the oral-nasal-pharyngeal site can be treated, provided the patient can remain in apnoea for about 40 s or has been intubated. Owing to charlatans' false claim that direct IV gas administration could cure HIV infection, this route, in spite of having caused many accidents and deaths, is still used in third-world countries. Even though death is due to oxygen embolism and not to ozone toxicity, it must be proscribed because there are other safe methods for ozone administration.

Regarding the SC administration, ozonetherapists treating lipodistrophies must be warned to inject small volumes (1–2 ml) of gas (ozone concentration: 2–3 mcg/ml) in multiple sites for a total of only 80–100 ml. During the successive rest of about 30 min, a gentle massage with ozonated oil can be performed on the injected areas. This is already somewhat dangerous but it has never caused death as it has occurred after injecting 300–400 ml of gas. Intraperitoneal and intrapleural administrations have been hardly used by practitioners but they are of great interest for treating life-threatening peritonitis, empyema, peritoneal and pleural carcinomatosis and chronic viral hepatitis in patients undergoing peritoneal dialysis.

Accidental and war trauma, burns and all sorts of acute and chronic cutaneous infections can be proficiently treated with ozonated water and oil that, in comparison to conventional creams, deserve great attention. The topical use of ozone in chronic and torpid ulcers and wounds present in diabetic patients and elderly people allows such a rapid improvement and healing to promote ozone to the rank of "WONDER" drug.