Ozone Therapy in Critical Patients. Rationale of the Therapy and Proposed Guidelines

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SUMMARY – In combination with the most suitable orthodox therapy, there are rational bases for justifying the use of ozone therapy in critical patients. This approach is difficult to implement in intensive care units, not for technical reasons, but because ozone therapy is regarded with suspicion and scepticism. However, assuming that appropriate permission and informed consent are obtained, which is the best way to proceed? We should aim to improve oxygen delivery to vital organs and ischemic areas and to support respiratory, cardiac and renal functions. If the patient's metabolic conditions are not excessively deteriorated, within 3-4 days of daily ozonated autohemotherapy treatments the increased synthesis of antioxidant enzymes and the induction of heme-oxygenase-1 may reduce the chronic oxidative stress simultaneously caused by infection-inflammation-tissue necrosis and dysmetabolism. We suggest some guidelines with the proviso of being flexible for each clinical case. The aim is not to achieve a scientific result but to save human lives.

Introduction

Visiting an ordinary intensive care unit, one can observe a heterogeneous group of patients, all at risk of losing their lives owing to traumatic events, severe burns, stroke, gangrene of the limbs, abdominal or pulmonary infections with various degrees of septic shock. We have often wondered if an intensive application of ozone therapy combined with the best conventional therapies may improve the prognosis [1]. However, at Siena hospital the chief doctor has been always concerned about the legal aspects because if the patient dies he will be accused of having used a non-validated therapy. The Ethical Committee also refuses to give permission for a trial because there is not yet any prospect that ozone therapy could represent a valid support.

Recently, Dr. Brito urgently requested a scheme and schedule for treating a critically ill patient with ozone therapy. The patient was a Brazilian colleague who presented a multiple critical dissection of the aorta. Luckily an experienced surgeon was able to correct it by placing an aortic prosthesis, an aortic valve prosthesis and suitable stents in the aortic descendent and thoracic aorta. The patient was under extracorporeal circulation for about six hours and although he was aided by multiple blood transfusions (40 units) he developed a critical situation with lung shunt, pneumonia, fever and serious respiratory difficulties documented by very poor respiratory parameters and a gram negative bacterium on bronchoscopy aspiration. Fortunately, Dr. Brito was a dear friend of the patient, and a disciple of ozone therapy. Having read section 15 in my latest book1 concerned with ozone therapy in emergency conditions, he decided that it was worthwhile to combining the orthodox therapy with ozone therapy. After obtaining prompt permission from the director of the intensive care unit, on the basis of the family's request, an informed consent form signed by the family members and a special authorization from Ministry of Health regulatory agency on medical practice, he performed four major ozonated autohemotherapy (O-HAT) treatments daily for three consecutive days (October 4-6, 2005), using a blood volume of 200 ml each time and an ozone concentration of 40 mcg/ml on the first day and 25 mcg/ml on the 2nd and 3rd days. As the patient conditions started to improve, he reduced the number of treatments to two on the fourth day and to one daily for the following week. The patient had a remarkable improvement, characterized by normalization of body temperature

This paper is dedicated to the memory of Dr. Edison de Cesar Filippi, the most experienced ozone therapist in Brazil.

and improvement of respiratory parameters. He was then moved from the intensive care unit to a regular room, in fairly good health, walking, eating, and starting working on his laptop. Once all intravenous catheters were removed because they were no longer necessary, autohemotherapy was stopped. Moreover, because of the recent extensive surgery, it was decided to stop heparinization to avoid bleeding at surgery sites. This may have been an untimely decision because he had a sudden stroke with high intracranial pressure probably caused by an embolus from the heart or aorta. Any further attempt to save him was unsuccessful due to extensive brain swelling and cerebral death. Unfortunately this outcome is fairly frequent in patients with severe vascular disease.

What could be the role of ozone therapy and was it reasonable to undertake it? Dr G.S. Brito, who closely followed the patient and performed the ozone therapy during the first phase, is convinced that ozone therapy corrected a dangerous post-operative course. Needless to say, the initial surgery and conventional treatments were absolutely indispensable.

If clinical conditions tend to further deteriorate, before multiorgan failure develops, a prompt and appropriate use of ozone therapy may improve the situation even though its intrinsic validity remains a matter of opinion. Nonetheless, in such cases, the scientific rigor is less important than the patient's life. According to Paragraph 32 of Helsinki Declaration the assumption is: In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Dr G.S. Brito felt that we should propose a guideline taking into account the dysmetabolic and most frequent septic conditions of critically ill patients.

A brief analysis of the problem

Owing to the extreme variability of the aetiology and pathogenesis of the above indicated pathologies, it is reasonable to ask if they share a common denominator which may justify the use of ozone therapy. Is it inflammation, or tissue degeneration, or infection? We feel that the most important and common problem is the presence of chronic oxidative stress (COS) which is a persistent and progressive imbalance between decreasing antioxidants and prevailing oxidants, able to induce a generalized cellular apoptosis and death of the patient. During an infection and/or a chronic inflammation, leukocytes and macrophages generate excessive amounts of reactive oxygen species (ROS, such as anion superoxide, hydrogen peroxide, hypocloric acid) that unselectively destroy pathogens as well as normal cells. Ozone therapy is currently the only procedure able to block and reverse this negative process because it can:

1) Enhance the transport and release of oxygen in ischemic areas. One may think that reperfusion may further damage hypoxic tissues, but if the degeneration has not gone too far, the messengers generated by ozone, namely the lipid oxidation products (LOPs), can, after binding to cell receptors, stimulate the synthesis of antioxidant enzymes such as superoxide dismutase (SOD), catalase (Cat), glutathione peroxidase, reductase and transferase (GSH-Px, Red. and Tr.) [2-6]. Moreover and most importantly, small calculated and transitory acute oxidative stress is one of the best stimuli for inducing the synthesis of some acute oxidative stress proteins, of which the most protective is the inducible heme-oxygenase-1 (HO-1) [1]. This enzyme (OSP-32) allows the degradation of heme from over-abundant hemoproteins and hemoglobin and results in the formation of biliverdin (hence bilirubin that is a valuable lipophilic antioxidant) and carbon monoxide (CO). The concomitant co-induction of ferritin, due to the release of iron, allows the beneficial sequestration of redox-active iron, thus avoiding formation of hydroxyl radical ($OH^{\cdot}$) by the Fenton reaction. Since 1978, the properties and protective effects of HO-1 overexpression have been described in over 3600 publications! It is impossible to enumerate all of the functions of this Herculean enzyme able to prevent or improve different pathological conditions.

2) During infusion of the ozonated blood into the donor, LOPs enter into contact with the vast expanse of the endothelium and stimulate an increased synthesis of nitric oxide (NO) via NO-synthase and arginine [7]. NO (and NO-thiols) and CO are the crucial physiological gases able to activate guanylate cyclase, so that the release of cyclic GMP enhances the vasodilation. The combination of these processes can, in not too advanced diseases, reduce infection, inflammation and cell degeneration.

3) Ozonation of blood ex vivo, by the controlled release of small amounts of the generated

hydrogen peroxide, allows a mild activation of neutrophils and the induction of the production of some cytokines [8-12]. After re-infusion of the ozonated blood, the activated or primed leukocytes migrate all over the body and can slowly improve the response of the adaptive immune system. Obviously, with the crucial help of appropriate antibiotics, even chronic infections can be controlled.

4) Some of our experimental data suggest that stimulation of platelets [13,14] and endothelial cells [7] by LOPs may favour the release of growth factors and autacoids, one of which may be prostacyclin. Surprisingly, LOPs may also inhibit cyclooxygenase II with the beneficial consequences of reducing hyperpermeability, edema and pain [15].

5) Once LOPs and nitroso-thiols reach the bone marrow microenvironment, they may activate metalloproteinase 9, a critical enzyme favouring the release of staminal cells. After their mobilization, these cells may enter the general circulation and home in infarcted areas. Although this idea has not yet been experimentally proved1, it is a likely possibility that must be pursued because it may acquire practical importance.

6) Ozonation of blood performed using sodium citrate (1 ml of citrate 3.8% solution/ 9 ml of blood) does not cause any dyscoagulation during slow blood infusion. Citrate is rapidly metabolized while heparin is less safe.

7) It is a general observation that the majority of patients undergoing ozone therapy report a feeling of well-being and euphoria. Although we have no experimental data, it has been speculated1 that by influencing cerebral, hypothalamic neurons and endocrine cells, LOPs may induce the release of some hormones (ACTH, cortisol, dehydroepiandrosterone, serotonin, endorphins) able to induce a reduction of pain and a feeling of wellness.

8) Provided that ozone therapy is performed correctly, after millions of treatments performed all over the world during the last three decades, there is no record of acute or chronic toxicity1. Against scepticism and the dogma that "ozone is always toxic", we know that the ozone dose (calculated as the product of the ozone concentration per gas volume), representing the acute stressor, must be perfectly calibrated against the potent antioxidant capacity of blood in such a way as to never overwhelm it. Within the established therapeutic window (10-80 mcg/ml ozone per ml of blood), no more than 30% of the antioxidant capacity of blood is oxidized during the ozonation reactions and is rapidly (in about 20 min) reconstituted by a very efficient biochemical recycling of antioxidants [1,16].

9) According to a Cuban study, ozone may inhibit platelet aggregation, and at least theoretically, had ozone therapy been continued, it may have avoided thromboembolism in our case.

In conclusion, each autohemotherapic treatment, equivalent to a precisely calculated chemical shock, appears able to trigger a multitude of biological processes relevant for correcting the complex pathology present in critically-ill patients. The consequent possible correction of the chronic oxidative stress is particularly important.

How and when to perform ozone therapy. Tentative guidelines

We propose to perform the following procedures:

Major O-HAT. Depending on the hemodynamic status of the patient, Major O-HAT can be carried out by collecting from 50 up to 225 ml of venous blood in a sterile glass bottle (250-500 ml) under vacuum. Sodium citrate solution (3.8%) must be added to the bottle before the blood in the proportion of 1:9 ml blood. To avoid any risk of haemorrhage, heparin must be used cautiously by first ascertaining the coagulation parameters. The gas volume must be added in a 1:1 volume ratio using an initial ozone concentration of 10 mcg/ml per ml of blood. Five minutes of slow mixing to avoid foaming is sufficient to complete the ozone reaction before re-infusion of the ozonated blood into the donor. The ozone concentration can be slowly increased to 15- 20-25 mcg/ml during the next few days, but, because the patient is under COS, a higher concentration of ozone should be avoided because more deleterious than advantageous. Frequency of O-AHT can be up to three (about every 8 hours) on the first few days and then, if the patient improves, it can be reduced to two and one.

Minor O-AHT. Very simply, the residual 3-4 ml of blood remaining at the end of the infusion tubing during each O-AHT can be withdrawn in a 10 ml syringe just filled with 5 ml of gas (ozone concentrations at 80-100 mcg/ml for a total dose of 400- 500 mcg). After inserting a G21 needle, the blood is rapidly mixed with the gas by rotating the syringe for 1-2 min and then promptly injected intramuscularly (glutei), with the foam. The very high ozone concentration is purposely used to provoke some hemolysis in order to activate the induction of OSP, particularly heme–oxygenase-I. We suggest the same frequency of administration indicated for major AHT. This i.m. injection is intended to act as a minor acute oxidative shock that, in the hands of one of us (VB), greatly enhances the overall treatment.

An important and frequently overlooked aspect is the possibility that the critically ill patient, under pronounced COS, has a low blood antioxidant capacity. Although we are unable to correct the COS by administering megadoses of antioxidants, we must recommend intravenous administration of selected antioxidants immediately after the auto-hemotherapy treatment for 2-3 hours, hence 5-6 hours before the next O-AHT. For several reasons we suggest the infusion of human albumin (20% concentration), possibly diluted with 100 ml 5% glucose solution with additional 0.5 g of ascorbic acid. Unfortunately, N-acetyl-cysteine (NAC), the best precursor of reduced glutathione (GSH) is not yet available for infusion and therefore can only be administered per os, but this is rarely possible. A compromise is the i.v. infusion of GSH, which will transiently increase the plasma levels but will not increase the critical cellular level because, there is no membrane transport for GSH - at variance with what is commonly believed. Needless to say, depending on the hemoglobin content, we must be ready to perform allotransfusions because it will be useless to administer ozone therapy if the hemoglobin level falls below 11 g/dL.

If major O-AHT cannot be performed, as a last option we can resort to rectal insufflation of gas every 8 hours. A volume of 300-400 ml can be insufflated very slowly using an initial concentration of 5 mcg/ml that can be progressively increased to a maximum of 25 mcg/ml. In the case of abdominal or pulmonary lesions, particularly after trauma and infections, it is advisable to use intraperitoneal and intrapleuric insufflation of gas via, as usual, a polypropylene catheter. Ozone can exert both a direct disinfectant activity on these cavities as well as immunomodulatory effects without any discomfort or toxicity.

In the case of severe sepsis and/or septic shock the mortality can be as high as 50% and during the last two decades antibodies against endotoxin and TNF alpha as well as other approaches have yielded negligible results. However, several clinical trials have shown that infusion of recombinant human activated Protein C (Drotrecogin alpha activated) can markedly decrease morbility and mortality and therefore should be kept in mind because this protein reduces inflammation and overt dyscoagulation. Similarly, whenever surgery appears necessary, antibiotics and all the other supportive orthodox drugs must be applied because in our mind ozone therapy can only benefit the patient if used in combination.

Ozone may be able to reverse disseminated intravascular coagulation.

Conclusions

We have outlined a possible scheme and schedule for treating severely ill patients in intensive care units with ozone therapy. In spite of a minimal practical experience, there are good rational bases for suggesting the use of ozone therapy in combination with the best orthodox therapy to reduce the morbility and high mortality of these patients. It would be extremely gratifying if other ozone therapists would like to share their experience with us, so that we may be able to further improve the treatment. Once the patient, if mentally alert, and/or the family desiring to receive a specific treatment according to the Helsinki Declaration have signed an informed consent, the doctor should be allowed to proceed with the treatment. Dr. Brito is currently developing the design of a Phase I study for treatment of sepsis cases in the Intensive Care Unit of Trauma at the Emergency Surgery Department of his Medical School Hospital in Sao Paulo, Brazil.

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