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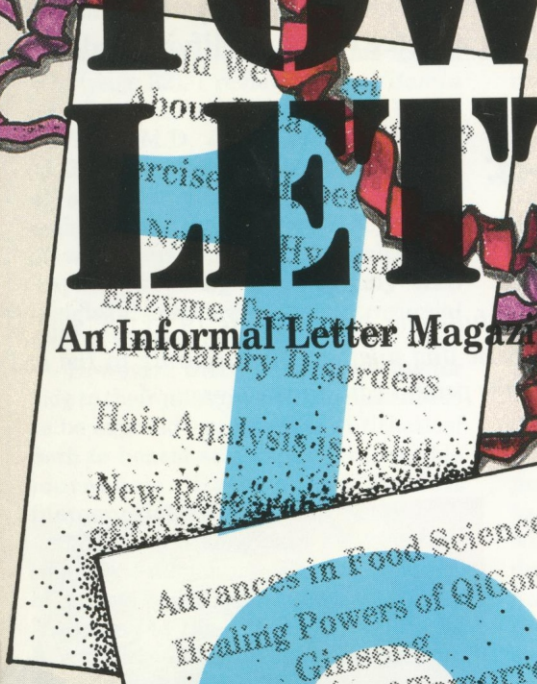
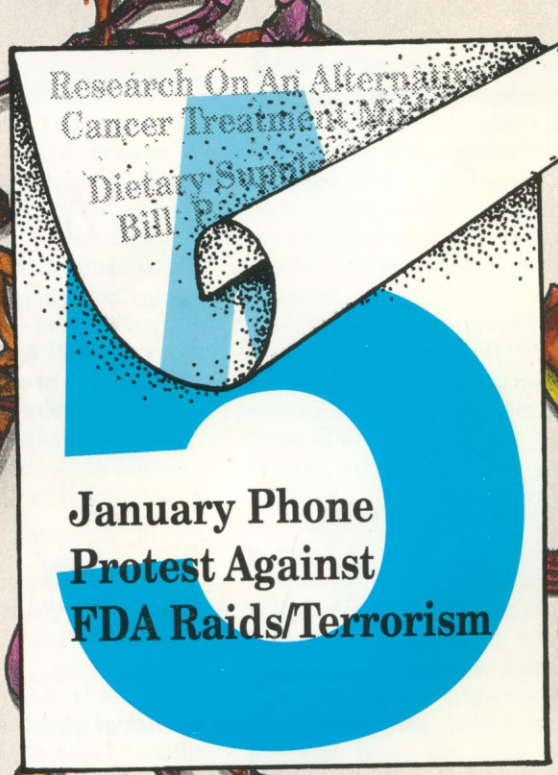


Chiropractic: A Profession at the Crossroads

Yeast Infections & Arthritis

Medicinal Ozone/ Oxygen Treatment for Sickle Cell Anemia

Lymphatic Therapy for Immune Disorders & Detoxification



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– Original Research –

Application of Medicinal Ozone/Oxygen in Patients with Sickle Cell Anemia

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Abstract

Sickle cell anemia is a genetic disease characterized by the sickled shape of erythrocytes in blood deficient in oxygen, where a modified hemoglobin, HbS, exists due to a single point genetic mutation, substituting valine at that position for glutamic acid which occurs in HbA, causing deoxy HbS molecules to form polymers. The crystallization, or intracellular polymerization of the molecules of HbS, occurs when these cells are deprived of oxygen, when oxygen partial pressure (pO2) falls below the threshold level at which sickling occurs. In this condition, the erythrocytes lose their normal elasticity and shape, increasing blood viscosity and aggregation, and impeding blood flow, and further reducing the availability of oxygen to the erythrocytes, producing vessel occlusive crises, infarctions, abdominal and muscular pains, ulcers, etc. This process is reversible in the early stages, for when the HbS molecule is reoxygenated the cell distortion disappears and the cell resumes its normal shape. The longer the period of time necessary for the reoxygenation of the molecules of HbS, the greater number of red cells die. Therefore, the partial pressure of oxygen and the promptness with which it is normalized are the determining factors for the symptoms to diminish and to disappear.

Currently, outside of Cuba (based, in part, on the results of this study), there is no effective treatment for this condition. There was no effective treatment for significantly raising blood pO2 without undesirable side effects, so it remained an unsolved problem. On the basis of some of the therapeutic properties of ozone (when introduced into the human body in other than the respiratory tract), particularly its ability to achieve rapid and significant increments in blood oxygen partial pressure, due to the enhancement of the erythrocytes capacity for oxygen absorption and delivery, allowing improvement in the rheological properties of blood at tolerable and non-toxic doses, an evaluation of the effectiveness of ozone/oxygen treatment for the timely resolution and/or the prevention of the vaso-occlusive crisis was made. Firstly, the enhancement of blood pO2 in ozone/oxygen treated samples above those treated with oxygen (neat) was demonstrated "in vitro" in normal blood-bank blood. Secondly, for the controlled clinical trial, 55 adult sickle cell anemia patients entering the hospital in crisis were studied. In comparison to the control group (N=25), the test group (N=30) demonstrated significant objective increases in arterial blood pO2, as well as reduction in the time for the resolution of crisis. During the six month follow-up, in which the test group was prophylactically treated with ozone once every two weeks, these patients suffered a much lower frequency of crisis. Those crises that occurred during this period were less severe in comparison to those of the control group. This treatment for sickle cell anemia crisis was approved by the Cuban Ministry of Health in November of 1990.

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Presented by Dr. Manuel Gomez at the 18th Annual Meeting of the National Association for Sickle Cell Disease, at The Children's Hospital of Philadelphia, May 24, 1993.

Application of Medical Ozone Therapy in Patients with Sickle Cell Anemia

Abstract

In patients with sickle cell anemia, the reduction in the availability of oxygen for the cells, produces painful crises, organ infarction, abdominal and/or muscular pains, ulcers, etc. On the basis of some medical properties of ozone, concerning ability to increase the rate and the capacity of absorption oxygen in erythrocytes, an evaluation about the effectiveness this treatment for the prevention and/or the timely resolution of the crisis was made. For the controlled clinical trial, 55 adult sickle cell anemia patients were studied, each suffering from painful crisis. Two groups were established: control group, comprised of 25 patients who received conventional treatment and ozone/oxygen treated group, comprising 30 patients who received the same treatment plus ozone therapy, by intra-rectal administration, during 15 sessions. The average time required for resolution of painful sickle cell crisis in ozone/oxygen treated patients was half the number of hours required to solve painful crisis in control patients. Frequency and severity of painful crises in sickle cell anemia patients who received ongoing ozone/oxygen therapy diminished in the six month follow-up period, in comparison with control group patients.

Introduction

Sickle cell anemia, a genetic disease which involves the sickle shape of erythrocytes, when blood oxygen tension is low, is represented by a modified hemoglobin, HbS, due to the substitution of glutamic acid by valine in the amino acid chain. The crystallization or intracellular polymerization of the molecules of HbS occurs when those cells are deprived of oxygen up to a partial pressure of oxygen (pO2) below the threshold level at which

the cells sickle. In these conditions, the erythrocytes lose their normal elasticity and shape, also losing their capacity to take and deliver oxygen and increasing the viscosity of the blood. This leads to a reduction in the availability of oxygen to the cells, producing painful crisis, infarction, abdominal and/or muscular pain, ulcers, etc. This process is reversible in the early stages, for when the HbS molecule is reoxygenated the cell distortion disappears and resumes its normal shape. The longer the period of time necessary for the reoxygenation of the molecules of HbS, the greater number of red cells die. Therefore, the increase in the partial pressure of oxygen and the promptness with which it is normalized are determining factors for the symptoms to diminish and disappear.[1] Attempts have been made to establish effective treatment for this disease, but their value and absence of side effects has not been confirmed in medical practice.[2-4]

Numerous reports have been published on the safety and clinical results obtained by the application of medical ozone/oxygen in diseases related to insufficient oxygen supply to tissues and various organs, and/or the disruption of its utilization in the cells. Ozone virucidal effect has been reported at dose levels at which no undesirable side effects take place, offering promise as a means to inactivate human retroviruses in human body fluids and blood products preparation.

Among the medical properties of ozone documented are the ability to increase the rate and capacity of oxygen absorption in erythrocytes and the activation of glycolisis in the cells via the pentose pathway. This enhances the production of 2,3 DPG, which is known to act as a coadjuvant of oxygen release from oxyhemoglobin at tissue level.[7,8] Both effects lead to significant improvement in oxygen supply to the body, demonstrated in vivo by the measurement of pO2 increase in arterial blood as well as the reduction in venous.[9]

In addition, the rheological properties of the blood improve, especially in regard to erythrocytes aggregation (preventing rouleaux formation and clumping) and membrane permeability and flexibility, because of the effect of ozone/oxygen on it. As a consequence of these effects, reduction of blood viscosity and enhancement of blood flow are achieved.[10-12]

Numerous preclinical experiments have been performed in vitro and in vivo to test possible ozone/oxygen toxicity related to the therapeutic methods and ways of administration according to which medical ozone/oxygen is currently applied. Controlled in vitro testing on the degree of hemolysis and "Heinz Body Formation" induced by the administration of ozone to blood at adequate dosage was performed,[13] not finding any significant effect, neither on the hemolysis level nor in the resistance of erythrocytes to further oxidative stress. These results are consistent with the fact that ozone stimulates several enzymatic redox systems responsible for cells protection against oxidation.[11]

Doses up to more than ten times the maximum therapeutic levels were tested for toxicity. These studies[14-21] comprised cytotoxicity, organs function, hematological parameters, histological studies by electron microscopy, teratogenicity and cytogenetic testing. All the results demonstrated the non-toxic nature of medical ozone/oxygen within the range of therapeutic dose levels when administered intravascularly, intramuscularly and intrarectally.

Based on the major role blood deoxygenation and hypoxia play in the onset and persistence of painful sickle cell crisis, and considering the established therapeutic properties of medical ozone/oxygen, and the absence of negative side effects, an evaluation of the possible effectiveness of this treatment for the prevention and/or the timely resolution of the crisis was made, by means of controlled in vitro and clinical trials. It was encouraged by our extensive successful practice in numerous Havana City Hospitals, fundamentally that regarding the treatment of patients suffering circulatory insufficiencies, diabetes and many other diseases related to insufficient supply of oxygen to tissue.[22]

Materials and Methods

Ozone/oxygen was obtained from a pure (medical grade) oxygen by means of a medical ozone generator (Ozomed, a device manufactured in N.C.S.R., Havana, Cuba), at a concentration of 50 mg ozone/L oxygen (ca. 3.7%).

The ability of ozone/oxygen to in vitro raise pO2 of normal bank blood was compared to that of pure medical oxygen. To each one of ten paired (5 + 5) blood samples (5mL each) contained in closed 10 ml vials, 2.5 mL of pure oxygen or ozone/oxygen mixture respectively were carefully bubbled through. Gasometric analyses were performed in test samples 5 minutes after gas administration and also in control untreated samples.

Preliminary clinical trials were performed comparing two modes of administration of medical ozone/oxygen: autohemotherapy (5 mg) and rectal insufflation (10 mg). Similar responses were obtained in both groups. Taking into account these results and considering the frequent difficulties encountered with the veins of these sickle cell patients, the intra rectal mode was chosen. Ozone was administered daily (5 days per week) for 3 weeks. For the controlled clinical trial, 55 adult sickle cell anemia patients were studied, each suffering from painful crisis in different degrees of intensity, who were admitted to the emergency service of the Institute of Hematology and Immunology, Havana, Cuba. Informed consent was gotten from patients before entering the study.

After resolution of the crises, a 6-month follow-up was performed in every patient. Two groups were established with patients selected at random:

Group 1: Control group, comprised of 25 patients who received conventional treatment with analgesics, vasodilators, and i.v. hydration (saline solution).

Group 2: Ozone/oxygen treated group, comprising 30 patients who received the same treatment plus ozone therapy.

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Table 1
Distribution by Sex and Age

	Sex			Mean Age (range)	
	Male	Female	Total	Male	Female
Group 1	11	14	25	26 (22-34)	25 (21-30)
Group 2	12	18	30	28 (30-36)	26 (21-32)

The distribution of patients by sex and age in both groups is presented in Table I.

There were not significant differences in age and sex among groups. Also both had similar mean values of hemoglobin, reticulocytes, fetal hemoglobin, hemoglobin S and oxygen partial pressure (pO2). No patient received a blood transfusion in the period of 6 months prior to this study. Severity of crisis were classified according to:

Mild crisis: Lasting not more than 12 hours; treated with analgesics, not needing i. v. saline solution for relief. Relatively low intensity pain, located in one or two body regions.

Moderate crisis: Within 12 and 24 hours duration. In addition to analgesics, also requiring continuous i.v. saline solution for relief. Moderate pain, localized in two or more regions in the body.

Severe crisis: More than 24 hours duration. Requiring analgesics, continuous i.v. saline solution and other therapeutic procedures (including whole blood transfusions). Intensive pain localized in 3 or more regions in the body.

Results and Discussion

The in vitro experiments with stored venous blood demonstrated considerably higher capacity for oxygen absorption in the samples treated with ozone/oxygen. These results are reported in Table 2

Table 2 shows pO2 and hemoglobin saturation values in control untreated blood, and those achieved in samples of the same blood after respective oxygen or ozone/oxygen administration. The relative rise (%) in pO2 obtained with ozone/oxygen nearly doubled that obtained with only pure oxygen. There were no significant differences in pH values among samples.

In the controlled clinical study comprising the aforementioned 55 patients, several hematological parameters were evaluated before and after treatment. These results are shown in Table 3.

Table 3
Parameters Measured in Arterial Blood of Patients of BothGroups Before and After Treatment

	Group 1 (25 patients)				**Group 2** (30 patients)			
	Initial		Final		Initial		Final	
	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD	$\bar{x}$	SD
pO2 (mm Hg)	71.2	± 3.1	72.5	± 2.5	71.5	± k	*84	± 4
Hemoglobin (g/dL)	7.7	± 0.5	7.7	± 0.4	8.0	± 0.5	8.4	± 0.4
Reticulocytes (%)	10	± 4	9.4	± 5.0	9.4	± 4.0	11	± 3
Hemoglobin S (%)	95	± 3	95	± 2	97	± 3	96	± 2

*p<0.05

Mean arterial blood pO2 value in control group patients remained virtually unchanged whereas a significant increase (17 %) was achieved for this parameter in group 2 (ozone/oxygen treated) patients after 15 treatments. The remaining blood parameters did not show any significant change in any group. It should be noted that the rise in pO2 was obtained with no reduction in hemopoiesis, (hemoglobin values remained stable), the latter reported to occur when hyperbaric oxygen is administered. Thus, ozone/oxygen therapy improved oxygen transport to tissue without adverse effects on the blood.

At the moment of inclusion in the study, the crises of patients included in the control and treated groups presented the characteristics shown in table 4.

Table 4
Distribution of Painful Crises Severity in Patients of Both Groups at the Inclusion of the Study

	mild %	**moderate %**	**severe %**
Group 1 (25) (control)	13 (52.0)	6 (24.0)	6 (24.0)
Group 2 (30) (ozone)	13 (43.3)	10 (33.3)	7 (23.3)

Table 2
Values of PO2 and Hemoglobin Saturation of Blood and the Same Blood After Oxygen or Ozone/Oxygen Treatment In Vitro

	Control n=5	**O2 Treated n=5**	**O3/O2 Treated n=5**
PO2	41 ± 1	73 ± 2	100 ± 2
PO2 rise (%) (above control)	—	78	143
HB saturation	60 ± 1	86 ± 2	93 ± 3

It was clinically observed, that by virtue of the better reoxygenation of blood in ozone-treated patients, demonstrated objectively by the rise in arterial blood pO2 (shown in Table 3) the promptness with which all crises (whether mild, moderate or severe) were resolved was significantly accelerated in the ozone/oxygen treated group as compared to the control group. These values are shown in Table 5.

Table 5
Average Time for Resolution of Painful Crises in Patients (hours)

	mild	moderate	severe
Group 1 (25) (control)	8	16	52
Group 2 (30) (ozone)	4	9	25

Table 6
Average Number of Painful Crises per Patient in the Six Month Follow-up for those Receiving Conventional Treatment (Control) or Ozone/ Oxygen Therapy

	mild %	moderate %	severe %	Total
Group 1 (25) (control)	2.5 (49.0)	1.2 (23.5)	1.4 (27.5)	5.1
Group 2 (30) (ozone)	1.2 (48.0)	1.0 (40.0)	0.3 (12.0)	2.5

After resolution of the initial crisis, ozone/oxygen treatments were continued prophylactically. They were administered one every 14 days over a period of 6 months to patients in the treated group. The number of subsequent crises per patient in this period were significantly smaller in the ozone/oxygen treated group, compared to the control group (receiving conventional therapy).

The proportion of severe crises also diminished very sharply in the treated group, compared to the initial proportion.

There were no adverse reactions observed during or after the administration of ozone in any of the patients treated. Additionally, it is of interest to mention that some of the patients in the treated group who suffered from associated clinical manifestations including: acute severe chest syndrome, priapism and duodenal ulcer, showed remarkable favorable resolution of such conditions.

Conclusions

- Medical ozone significantly raises blood pO2 in vitro.
- Ozone/oxygen therapy produces significant rise in arterial blood pO2 of patients, which is an objective effect, without significant alterations in other blood parameters. It does not inhibit hemopoiesis, as is the case with hyperbaric oxygen treatment.
- The average time required for resolution of painful sickle cell crises (mild, moderate and severe) in ozone treated patients was about half of that required to resolve painful crisis in control patients.
- PO2 values in the ozone/oxygen treated group during the follow-up remained high enough to significantly reduce the incidence of crisis as compared to the control group, regardless of whether their crises were classified as mild, moderate or severe.
- Frequency and severity of painful crises in sickle cell anemia patients receiving ozone/oxygen therapy during the six month follow-up was significantly lower in comparison with control group patients.
- No adverse reactions were observed objectively or subjectively in the patients who received ozone/oxygen therapy.

Sickle Cell Anemia

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News Release

James A. Caplan, President of CAPMED/USA, announces the completion of an order to supply Medizone International with five Labozon III ozone/oxygen systems with computer-based integrated control and precision photometric input/output/differential measuring and recording circuitry.

These delivery systems will be integrated with Medizone's patented hollow-fiber technology. They will be based at five university-based Italian hospitals where 300 persons will participate in AIDS and Hepatitis B trials over a period of approximately nine months in a Phase I human study to establish the safety of the modality. Subsequent trials will be designed to measure the effectiveness of ozone/oxygen in reducing the viral load of HIV infection and in reducing the severity of the opportunistic infections associated with AIDS.

Medizone, by letter of agreement with the Italian Scientific Society for Oxygen-Ozone Therapy (ISSOT), agreed to provide U.S. FDA-approved protocols for use by the research group, which was designated by the Italian Ministry of Health to sponsor the project. Dr. Joseph S. Latino, President of Medizone, has been invited to join the research group. Dr. Latino, along with Dr. Bernard J. Poiesz, a foremost U.S. retrovirologist, and others, authored an extensive study published in *Blood*, Vol. 78, No. 7, of October 1, 1991, pp. 1882-1890, "Inactivation of Human Immunodeficiency Virus Type I by Ozone In Vitro." This study reported that ozone could achieve an ll-log kill of HIV with minimal effect on Factor VIII (the blood clotting factor) activity. The data indicate that the antiviral effects of ozone include viral particle disruption, reverse transcriptase inactivation, and perturbation of the ability of the virus to bind to its receptor on target cells.

CAPMED and its German affiliate manufacture and supply precision medical ozone/oxygen generating and measuring equipment worldwide. CAPMED assists research groups with protocol development and implementation. CAPMED maintains completed protocol drafts for the study of Sickle Cell Anemia Disease, IIIV Disease, and HIV/AIDS/opportunistic infection.

In March of 1992, CAPMED received Orphan Drug Designation from the U.S. FDA for the use of ozone/oxygen for the treatment of Sickle Cell Anemia Disease. CAPMED initiated clinical trials in cooperation with the National Institute For Scientific Research, Havana, Cuba, the Institute of Hematology and Oncology, Havana, Cuba, and the Salvador Allende Clinic, Havana, Cuba. These trials were carried out in the years 1989, 1990, and 1991, culminating in ozone/oxygen being approved by the Cuban Ministry of Health for general use in the treatment of sickle cell crises, the ulcers ensuant to sickle cell disease, and for the prophylactic treatment of the disease. The safety and efficacy established in these trials led to the use of ozone/oxygen in the general population for healing wounds and diseases of the extremities (e.g., diabetic leg ulcers), where below or above knee amputation would be otherwise indicated.

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