Ozone Submission

History

- Benedict Lust, the founder of Naturopathic Medicine, in his Directory and Buyers guide fro Drugless Therapy 1918-19 documented the use of Ozone in Naturopathic Medicine
- H. Lindlahr discusses the use of ozone therapy in Nature Cure in 1925 on pages 145 (Lindlahr, 1913)
- John Henry Clarke discusses in A Dictionary of Practical Materia Medica 1900, Oxygenium and Ozonum applied in non homeopathic dosages (Clarke, 1902)
- Nature Doctors published in 1994, "Dr. William A. Turska who was chairman of the International Council on Naturopathic Philosophy…like Arno Kroegler (who practiced in Kitchener, Ontario), a true eclectic who does not shy away from methods, even those controversial among his peers, such as ozone therapy, hernia injection therapy and the wet blood drop test, he became a prototype of the modern naturopathic physician." (Kirchfeld & Boyle, 1994)

- Christian Freidrich Schonbein (1799-1868)
    - The founder of ozone, it was named from the Greek “ozein” meaning “to smell”
    - 1832 he published a book " The Production of Ozone by Chemical Means," (Erzeugung des Ozons auf chemischem Wege)
    - Author of 343 scientific publications in 837 edtions
    - 1857 the first medically used ozone generator constructed, which Kleinmann carried out his bacteriological trials on pathogenic germs and the first ozone insufflation
    - In October 18, 1999 Switzerland honoured the father of ozone, by printing a special stamp depicting ozone
  - 1857: First ozone generators were developed by Werner von Siemens in Germany
  - 1870: The first report of ozone being used therapeutically to purify blood by C. Lender, Germany
  - 1885: *The Florida Medical Association* published “*Ozone*” by Dr. Charles Kenworth, M.D., detailing the therapeutic uses of ozone
  - 1893: The world’s first water treatment plant using ozone was installed in Ousbaden, Holland
  - 1896: Nikola Tesla patented his first ozone generator. Tesla was also the inventor of the AC current
  - Erwin Payr (1871-1946)
    - Surgeon
    - 1935 published a 290 page report entitled, "Treatment with ozone in surgery" (Uber Ozonbehandlung in der Chirurgie) at the 59th Congress of the German Surgical Society in Berlin
  - 1902: In *“A Dictionary of Practical Materia Medica”,* J.H. Clarke, describes the successful use of ozone in treating anemia, cancer, diabetes, influenza, morphine poisoning, canker sores, strychnine poisoning, and whooping cough” (Clarke, 1902)
  - 1911: *“ A Working Manual of High Frequency Currents”,* Dr. Noble Eberhart M.D., head of the Department of Physiologic Therapeutics at Loyola University. He used ozone to treat

tuberculosis, anemia, chlorosis, tinnitus, whopping cough, asthma, bronchitis, hay fever, insomnia, pneumonia, diabetes, gout and syphilis (Eberhart, 1919)

- 1913: *The Eastern Association for Oxygen Therapy* was formed by Dr. Blass and some German associates
- 1920: Dr. Charles Neiswanger M.D., the President of the Chicago Hospital College of Medicine published *"Electro Therapeutical Practise".* Chapter 32 was entitled *" Ozone as a Therapeutic Agent"* (Neiswanger, 1898)
- 1926: Dr. Otto Warburg of the *Kaiser Institute in Berlin*, announced that the cause of cancer is the lack of oxygen at the cellular level. Metabolism of a cancer cell was like that of a plant cell, which thrives on carbon dioxide and gives off oxygen as its waste product
- 1929: *"Ozone and Its Therapeutic Action"* was published in the US, listing 114 diseases and how to treat them with ozone. The authors were the heads of all the leading American Hospitals
- 1931 & 1944: Dr. Otto Warburg was awarded the Nobel Prize in biochemistry. He was also nominated for a third. He is the only person to ever receive two Nobel Prizes for Medicine
- E.A. Fisch (1899-1966)
    - Dental surgeon
    - Recorded his experience with ozone
    - 1950 prepared a comprehensive doctoral thesis on the subject
    - The patent for the apparatus bearing the name CYTOZON, now used in modern ozone generators for dental medicine, was applied fro by E.A. Fisch as the first piece of laboratory equipment
- Joachim Hansler (1908-1981)
    - Studied physics, mathematics and chemistry and together w/ Hans Wolff took up medical work w/ ozone
    - Patented an ozone generator capable of delivering accurate, medical ozone applications
    - OZONSAN, was his creation and this founded the basis for modern therapy w/ medical ozone
- Hans Wolff (1927-1980)
    - General practitioner, published the book "Medical Ozone" in 1979 and training many doctors in ozone therapy
    - Introduced techniques of major and minor autohemotherapy
    - Together w/ J. Hansler, they founded the Medical Ozone Society (Arztliche Gesellschaft fur Ozontherapie) in 1972, it has been renamed in 1993 the Medical Society for Ozone application in Prevention and Therapy
- 1933: *The American Medical Association*, headed up by Dr. Simmons set out to destroy all medical treatments that were competitive to drug therapy. The suppression of ozone began there and continues today
- 1979: Dr. George Freibott began treating his first AIDS patient with ozone
- 1980: The prestigious *Journal of Science, Vol.209, Aug 22*, published a paper entitled: *OZONE SELECTIVELY INHIBITS GROWTH OF HUMAN CANCER CELLS.* Human lung, breast, and uterine cancer was exposed to ozone at concentrations of 0.3-0.8 PPM, well within the non-toxic limits
- 1990: Cubans report their success in treating glaucoma, conjunctivitis, and retinitis pigmentosa with ozone
- 1992: Russians revealed their technique of using ozone bubbled into brine to treat burn victims with astounding results

- After 125 years of usage, ozone is a recognized modality in many nations including: Germany, France, Italy, Russia, Romania, Czech Republic, Poland, Hungary, Bulgaria, Israel, Cuba, Japan, and Mexico
- Over 6,000 medical papers exist in the world medical literature proving ozone's efficacy in the treatment of disease in tens of thousands of patients, yet it has been ignored in North America primarily because it cannot be patented
- German ozone therapists' survey of 5,579,238 ozone treatments on 384,775 demonstrated a side effect rate of only 0.0007% of which were only minor and not even remotely life-threatening.
- Over 1 million patients a year are hospitalized in the US alone, due to side effects of prescription medications, of which over 100,000 die from such reactions. Yet if one person in the US dies even indirectly from the usage of a vitamin or herbal product, the FDA is quick to remove these products for future use

(Viebahn-Haensler & Lee, 2002)

Ozone

- Ozone is a chemical compound consisting of 3 oxygen atoms, a highly energetic form of normal (diatomic) atmospheric oxygen
- At room temperature, O_3, is a colourless gas w/ a characteristic odour (ie. after a thunderstorm)
- Discovered by the German chemist Christian Friedrich Schonbein (1799-1868)
- Ozone is a protective layer approximately 20-30km from the earth's surface
- It absorbs most of the UV radiation (<290nm) emitted by the sun, UV A (316-400nm) responsible for suntan and bands B and C (from 100 up to 315nm) which are far more mutagenic and responsible for enhancing skin aging and carcinogenesis
- Due to air turbulence, ozone is capable of penetrating to layers closer to the earth
- Under the action of UV light on nitrogen oxides, ozone is formed in the presence of oxygen and so ozone concentration is used as an indicator for pollution and thus ozone has been given a bad name, because people now assume that ozone is the cause of pollution and not the by product
- Ozone is an irritant to the respiratory system
- An extremely powerful oxidizing agent and a highly effective disinfectant, it is used throughout the world in water treatment installations

  (Viebahn-Haensler & Lee, 2002)

Ozone therapy

- Medical ozone is a mixture of pure ozone and **pure** oxygen
- Ozone is a substance which is not "metabolized" per se, nor does it form any residues; its metabolic mechanism lies in a stimulation of the organism's inherent processes

  (Viebahn-Haensler & Lee, 2002)

Properties and effects

- Medical ozone is bactericidal, fungicidal and virostatic properties
- Used in disinfecting infected wounds as well as in bacterially and virally produced diseases
- Stimulates the circulation
- Immunostimulatory, enhancing cytokine, interferon and interleukin response

  (Viebahn-Haensler & Lee, 2002)

Indications

1. Circulatory disorders
2. Viral related diseases such as hepatitis and herpes
3. Infections and inflammatory conditions such as colitis, burns, gangrene etc.
4. Immune deficiency or weakness
5. Complementary therapy in environmental medicine, and oncology

(Viebahn-Haensler & Lee, 2002)

Application Form

- **Extracorporeal blood treatment (Major Autohemotherapy)**
  - 50-100ml of the patient's own blood is withdrawn, enriched externally w/ an exactly defined quantity of ozone (with disposable sterile materials and containers)
  - The ozone reacts completely (at a rate of 100%) w/ the RBC and WBC and thus activating the necessary metabolism
  - It is this "activated" blood that is re-introduced into the patient's system using a normal drip unit
  - Technically, the "ozone" used is, in actual fact, a mixture of purest ozone and medical oxygen (0.05-5% (Vol.) ozone = 1-100 µg/ml + 99.5-95% oxygen)
  - The dosage ranges are specifically determined using a generator from anywhere between 10-40 µg ozone / ml blood
  - The extracorporeal treatment of a patient's blood with medical ozone is a risk-free method.
  - Ozone is a substance which is not "metabolized" per se, nor does it form any residues; its metabolic mechanism lies in a stimulation of the organism's inherent processes

(Beck, Wasser, & Viebahn-Hänsler, 1998)

Indication	O_3 quantity in µg	Treatment frequency	No. of treatments
1. Arterial circulatory disturbances			
Cerebral and peripheral, stage II	800? 2000 µg per 50 ml blood	2 x per week	Series of 10 treatments 2? 3 x per year
Stage III and IV	3000? 4000 µg per 100 ml blood	daily at first, then 2 x per week	
2. Immunoactivation			
Geriatrics	800? 2000 µg	2 x per week	Series of 10 treatments 2 x per year
Preventive vs. infection	800 - 1500 µg	2 x per week	Series of 6 treatments 2 x per year
Adjuvant in cancer therapy	500 µg	2 x per week	Series of 10 treatments several times per year or : 2 treatments per month after the 1st treatment series (continuously)
3. Infections			
Hepatitis, A, B, C			several series
Acute	3000 µg in 70-100 ml blood	daily	as per control
Subsiding	1500-2000 µg	2 x per week	as per control
Chronic	1000-1500 µg	1? 2 x per week	as per control
Herpes zoster			
Acute stage	3000 µg in 50? 100 ml blood	daily in the 1st week	1 series of 10 treatments
post acute	1500-2000 µg in 50 ml of blood	2 x per week	as per control

(Beck et al., 1998)

Materials (MAH)

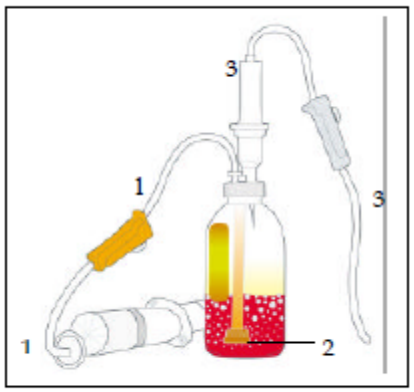
From a quality assurance and quality control point of view, the high reactivity of ozone with organic substances requires a careful selection of materials needed for the different types of medical equipment:

- Only special materials can be used in ozone generators, such as Teflon (PTFE), specially anodized aluminium (anti-friction), V4A-quality stainless steel (in long-term use, V2A quality is subject to surface changes), glass and ceramics
- For application systems only "ozone-resistant" materials such as glass, polyethylene (PE) ,polypropylene (PP) , and PTFE come into the question

- Other plastics, especially for syringe pistons, must be silicone-coated
- Medical plasma flasks as used for reinfusion should be made of glass only; the plasma bags made of soft PVC in general hospital use are NOT ozone-resistant.
- The use of plasma bags made of non-ozone-resistant, soft polyvinylchloride (PVC) is to be rejected. This is because reactions between the ozone and the plastic material can occur producing xenobiotic and/or toxic substances, especially during O3 blood treatment requiring up to 5 minutes to obtain the proper effect. The substances arising from a decomposition of the softening agents in the plastic, such as e.g. hydrogen peroxide or phthalic acid esters are not only able to distort the desired effects of ozone, but also damage the patient's health
- For preparing and storing ozonized water, containers made exclusively of glass are to be used, these having a small volume (e.g. 250 ml) as far as possible; they should be completely filled and well sealed [also with O3-resistant material]
- Use sterile, siliconized, 50-ml disposable syringes (ozone half life: 55 min)

Method (MAH)

- After closing the valves on both lines (infusion line [3] and germ stop [1]), connect the infusion line to the flask by piercing through the large circle in the stopper [4], connect the "germ stop" filter in the same way through the cross marked on the stopper (connection with microbubble system [2]).
- Attach a long cannula) to the opened sodium citrate ampoule, allow 10 ml to be drawn into the vacuum flask
- Withdraw 50 ml ozone/oxygen gas mixture from the outlet valve on the ozone generator using a sterile disposable syringe with a preconnected bacterial filter.
- Connect the syringe filled with 50 ml gas to the cone of the "germ stop" filter.
- Remove 50 ml of the patient's blood intravenously so that it is transferred to the vacuum flask, allow the ozone/oxygen mixture to be drawn up via the bacterial filter in the "germ stop" device, producing an even passage of the gas through the blood in the form of minute bubbles (microbubble process).
- Turn the flask over, remove the injection system venting the vacuum flask, and reinfuse the ozone-treated blood.



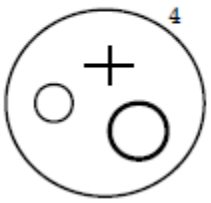


Fig. 3. MAH acc. [9]
1. "germstop" with bacterial filter
2. micro-bubble system
3. transfusion set
4. stopper, surface view

(Beck et al., 1998)

Application Form

- **Rectal/Vaginal insufflation**
    - This is one of the oldest forms of application in ozone therapy
    - Increasingly being used as a systemic therapeutic form and an alternative to MAH in patients whose veins are compromised
    - Ozone is directly absorbed by the intestinal membrane/vaginal lining entering into the portal circulation
- **Indications (Insufflation)**
    - Ulcerous colitis
    - Proctitis, stages I and II
    - Anal fistulae and fissures
    - Indications cited for MAH
    - Hepatitis B and C
    - For immunomodulation (complementary method in oncology)
- **Method (Insufflation)**
    - An ozone supply container with lock valve, dosing bag with non-return valve, connecting tube with luer/luer lock or 50 ml silicone-coated disposable syringe and rectal catheter
    - 10-25 µg ozone/ml oxygen gas mixture, volume 150-300 ml

Application Form

- **Topical application**
    - Has been utilized as a disinfectant since World War I
    - Ozonized water/olive oil good for
        - Skin lesions
        - Burns
        - Eczema
        - Acne
        - Cold sores
- **Method (Ozonized water)**
    - For 5-15 minutes, allow an ozone/oxygen gas mixture at an O3 concentration = 100 or 60-80 µg/ml to pass in the form of minute bubbles through 1 litre distilled water
    - In distilled water, the half life of ozone is approx. 10hrs at room temperature, the concentration remaining approx. 18-24 µg/ml at 20 °C [68°F]. In the refrigerator, ozonized distilled water can be kept for approx. 5 days
    - Overdosage is not possible, as the quantity of ozone used is limited by its solubility in water,
    - The healing time for primary scars is shortened and irritation-free
- **Bagging (Transcutaneous ozone immersion)**
    - Used to treat gangrene, diabetic foot ulcers, bedsores, burns, and infected wounds
    - The bag is placed around affected area and sealed effectively
    - The output tube from the ozone generator is placed through the top of the bag and humidified ozone enters the bag

Application Form

- **Intraarticular ozone injection**
    - Injection of ozone into the joints in the treatment of inflamed joints
    - Low-pressure (subatmospheric) ozone treatment in acute and chronic, painful joint conditions represents one alternative treatment method which provides rapid pain relief, decongestion, subsidence of bruises (haematomas), a reduction in temperature and an

improvement in motility. It involves knee and shoulder joints presenting chronic pathological symptoms
(Beck et al., 1998)

Indications:

-**Arterial circulatory disorders**
- Peripheral arterial circulatory disorders
- Cerebral circulatory disorders

The **Fontaine classification** is a method by which peripheral artery disease is clinically classified. Peripheral artery disease may be asymptomatic or symptomatic and the spectrum of symptoms is classified according to the **Fontaine classification**. The Fontaine classification is not usually used in everyday clinical practice. On the other hand, it is useful for research purposes. There are five Fontaine stages (actually there are four, and one subtype):

1. Stage I – Asymptomatic. Of note: Fontaine stage I does in fact describe patients who are *for the most part* asymptomatic. Careful history may actually reveal subtle and non-specific symptoms such as paresthesias. Physical examination may reveal cold extremities and other signs of "subclinical" peripheral artery disease. More examples include bruits over blood vessels and lack of normal pulses.
2. Stage II – Intermittent claudication. This stage takes into account the fact that patients usually have a very constant distance at which they have pain:
   Stage IIa – Intermittent claudication after more than 200 meters of pain free walking.
   Stage IIb – Intermittent claudication after less than 200 meters of walking
3. Stage III – Rest pain. Rest pain is especially troubling for patients during the night. The reason for this is twofold: First, the legs are usually raised up on to a bed at night, thus diminishing the positive effect gravity may have had during the day when the legs were dependent. Second, during the night the lack of sensory stimuli allow patients to focus on their legs.
4. Stave IV – Ischemic ulcers or gangrene (which may be dry or humid).

Pasted from <http://www.angiologist.com/fontaine-classification/>

Peripheral arterial circulatory disorders

- An investigation involving 152 patients was reported on by the Austrain ozone specialist *Rokitansky*, who administered preoperative ozone treatment to in-patients at a large Viennese hospital (1974-1980) results indicated in the two tables below
(Rokitansky, 1982)

Fontaine stage	N	Success	Improved	No success
II	62	54 (87.1%)	6 (9.7%)	2 (3.2%)
III	51	36 (70.6%)	11 (21.6%)	4 (7.8%)
IV	39	21 (53.8%)	10 (25.6%)	8 (20.6%)

Fontaine stage	Success	Improved	No success

II	Walking distance >1000m	>400m	Same state or aggravation
III	>800m No pains at rest	>300m Occasional pain	Same state or aggravation
IV	>500m and gangrene completely healed	Amputation of toes or front part of foot with healing of stump	Same state or aggravation

Mattassi (1981) reported results on 113 cases treated with ozone from the vascular surgery department at a Milan hospital, results indicated in table below. (Association, 1981; Mattassi, 1981)

Fontaine stage	N	Success	Improved	No success
II	48	8 (17%)	28 (58%)	12 (25%)
III	27	2 (7%)	18 (67%)	7 (26%)
IV	38	4 (11%)	16 (42%)	18 (47%)

Cerebral circulatory disorders

- Wasser utilized major autohemotherapy in a group of 43 patients w/ acute stroke in addition to hospital treatment

- Utilized 3000µg per treatment on a daily basis, results are below
- None of the patients died as a direct result of the stroke, all were spared the severest form of strokes effects
- Nuclear resonance (NMR) pictures of 9 patients, compared w/ those of the patients not treated w/ medical ozone, are noticeable for a particularly small scar in comparison which explains a lower incidence of functional disorders in these patients (Viebahn-Haensler & Lee, 2002; Wasser, 1995)

Restoration of physical functions, including fine motor control (T1)	Retention of general motor function, fine motor control absent (T2)	Typical spastic conditions need of care (T3)
N = 37	N = 6	-

- **Skin lesions**
    - Diabetic gangrene
    - Burns

Bedsores and ulcers

- Werkmeister carried out studies on 214 cases of bedsores over a period from 1975 through 1988
- In 40% of cases (85 patients) 80-100% of the wound could be closed, all of the patients were in a sever and/or advanced stage
- Low pressure ozone irrigation under the suction cup is the application of utilization (Werkmeister, 1995)

Diabetic skin ulcers

- The aim of this study was to investigate the therapeutic efficacy of ozone in the treatment of patients with type 2 diabetes and diabetic feet and to compare ozone with antibiotic therapy. A randomized controlled clinical trial was performed with 101 patients divided into two groups: one (n=52) treated with ozone (local and rectal insufflation of the gas) and the other (n=49) treated with topical and systemic antibiotics
- Patients were randomized to two different groups of treatment: 1) antibiotic therapy; 49 patients were treated with systemic antibiotic therapy (according to the microbe present), using the conventional method of treatment, with topical application to the lesion (for 20 days), and 2) ozone; 51 patients were treated daily with ozone (generated by an OZOMED equipment, Cuba), 20 sessions, by rectal insufflation (with an ozone dose of 10 mg, ozone concentration: 50 mg/l) and locally. For local ozone treatment, the lesion was covered with a plastic bag, sealed to the leg, which was then put under vacuum, in order to eliminate the air inside it. Afterward, the bag was refilled with ozone at a concentration of 60 mg/l. The patient remained with the plastic bag for 1 h. After that, the bag was removed and the lesion was covered with ozonized sunflower oil (Oleozon®).
- The efficacy of the treatments was evaluated by comparing the glycemic index, the area and perimeter of the lesions and biochemical markers of oxidative stress and endothelial damage in both groups after 20 days of treatment
- Ozone treatment improved glycemic control, prevented oxidative stress, normalized levels of organic peroxides, and activated superoxide dismutase
- The pharmacodynamic effect of ozone in the treatment of patients with neuroinfectious diabetic foot can be ascribed to the possibility of it being a superoxide scavenger. Superoxide is considered a link between the four metabolic routes associated with diabetes pathology and its complications. Furthermore, the healing of the lesions improved, resulting in fewer amputations than in control group. There were no side effects. These results show that medical ozone treatment could be an alternative therapy in the treatment of diabetes and its complications.
- The main variables considered were:

    1) Clinical evaluation of the lesions: a) Measurement of the area and perimeter of the lesions by means of a trace done on an acetate plate (planimetric analysis), under aseptic conditions, at the beginning and at the end of the study, and the change in both parameters with time. The resultant area and perimeter were quantified using a computer program (DIGIPAT). b) Qualitative clinical evaluation of the lesions. c) Length of hospitalization was the time necessary to obtain an aseptic lesion, with good granulation tissue and in a healing process or ready to receive a graft.

    2) Glucose levels, measured at the beginning and at the end of the study, taking into account that hyperglycemia is theprimary factor, were associated with diabetes and its complications.

    3) Secondary variables considered were: a) Serum levels of fructolysine, advanced oxidation protein products, nitric oxide, reduced glutathione, glutathione peroxidase, catalase, superoxide dismutase, total hydroperoxides, peroxidation potential and malondialdehyde. b) Side effects.

- A good result was considered when there was a decrease in: the area and perimeter of the lesion, the duration of hospitalization, and in levels of glucose, fructolysine, advanced oxidation protein products, malondialdehyde, peroxidation potential, and total peroxides. An increase in nitric oxide, reduced glutathione, glutathione peroxidase and an approach to physiological values of the ratio catalase / superoxide dismutase were also considered as good results. In the case of biochemical variables, laboratory data for healthy individuals (n=50) were taken as normal reference values (control group). This group of subjects corresponded in terms of age, sex and ethnicity with both groups of patients

enrolled in the study. Therapy was considered successful if 70% of the patients treated with ozone had a positive outcome, taking into account the main variables, and if this improvement was 20% higher than that in the patients treated with antibiotic therapy.

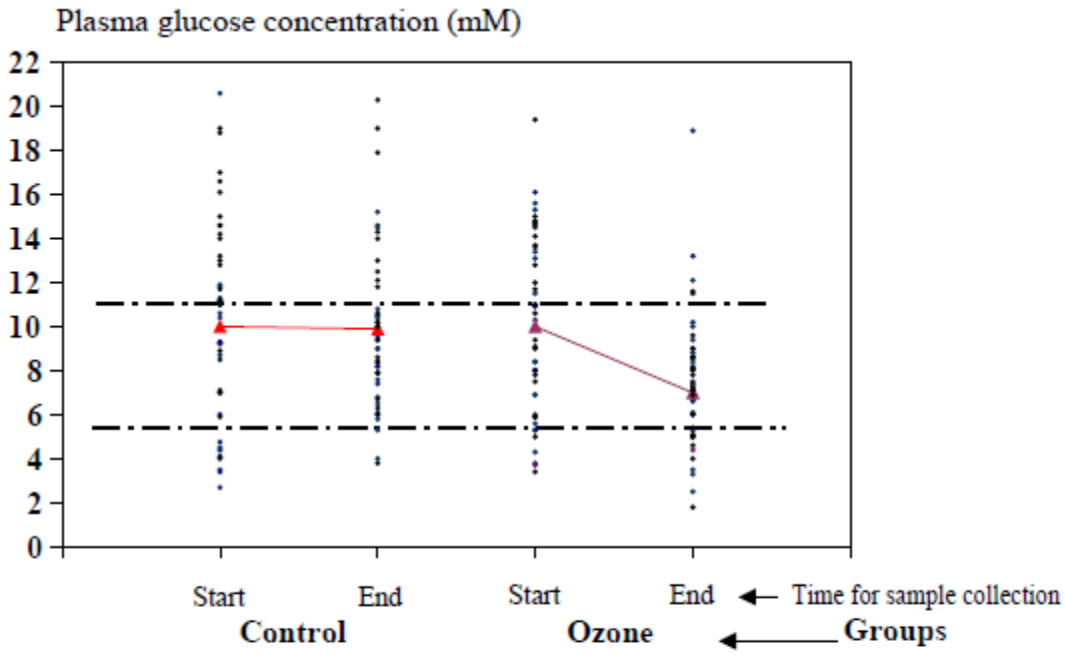


Fig. 1. Plasma glucose concentrations (mM), at the beginning and at the end of the study (20 days), for control (n=49) and ozone (n=51) groups. The continuous lines correspond to the mean glucose concentrations for each treatment. The discontinuous lines (—) represent the normal reference interval for Cuban people (3.33–8.88 mM).

Table 2
Measurement of the area and perimeter of the lesions, at the beginning and at the end of the study, the variation in both parameters with time, as well as the expected total recovery for both groups

Parameter		Start (X±SD)	End (X±SD)
Area (cm^2)	Antibiotic (n=49)	54.84±0.39	40.72±0.35
	Ozone (n=51)	57.97±0.52	23.31±0.36
	p^a	0.687	0.017
Perimeter (cm)	Antibiotic (n=49)	21.49±0.11	17.34±0.14
	Ozone (n=51)	18.49±0.14	12.62±0.13
	p^a	0.063	0.004
		Control (n=49)	Ozone (n=51)
Area reduction (%)	%	50.30±0,17	74.58±0.35
	p^b	0.017	
Perimeter reduction (%)	%	26.63±0.17	41.52±0.25
	p^b	0.000	
Healing rate with respect to area (cm^2/days)	X±SD	1.21±0.01	2.66±0.05
	p^b	0.005	
Healing rate with respect to perimeter (cm/days)	X±SD	0.24±0.00	0.34±0.00
	p^b	0.040	
Expected total recovery (days)[a]	X±SD	45±11	21±10
	p^b	0.002	

Start and End are the beginning and end of treatment (after 20 days) with ozone or antibiotics. Data are mean±S.D.
p^a is the probability between groups, at the same time of treatment.
p^b is the probability between different treatments.
[a] Expected Total Recovery is a criterion of healing according to the planimetric evaluation. It represents the expected days needed to achieve total healing (trend to zero of the area and perimeter of the lesions).

(Martinez-Sanchez et al., 2005)

- **Intestinal condition**s
    - Proctitis and colitis

Proctitis and colitis

- Knoch reported in 248 patients with stage I proctitis, rapid healing success was obtained in 199 patients. The rectoscopic findings showed significant improvement after a single treatment
- In 80 patients w/ stage I proctitis, after a series of 10 rectal ozone/oxygen insufflation, a remission time longer by more than 3 months was found in the patients of ozone/oxygen group (10.2 months vs 6.4 months) compared w/ 80 other patience suffering from the same condition who had been treated w/ salazosulfapyridin taken as a control group
- Rectal insufflation of 300ml ozone/oxygen gas mixture at a concentration of 20µg O_3/ml corresponding to 6000µg ozone per treatment

- Treatment was carried out 2x/wk whereby a total of 25 patients received 3 treatment series at intervals of 9.7 months on average
- 3 weeks after the end of treatment a medical/clinical exam was conducted including a sigmoidoscopy w/ biopsy of the rectal mucous membrane and subsquent histomorphological investigation
(Beck & Viebahn-Hänsler, 1995; Knoch & Klug, 1990)

- **Viral Infection**
    - Hepatitis C: Zacky found that ozone treatment reduced symptoms and normalized liver enzymes for a significant number of patients with chronic Hepatitis C. (Zaky et al., 2011)
    - Herpes simplex and herpes zoster (Mattassi, Bassi, D'Angelo, Franchina, & Sbrascini, 1981)

Vaginal candidiasis
- In 20 patients with recurrent candidal vaginitis, unsuccessfully treated with (Clotrimazol) average age 26yrs, all received treatment w/ ozonated olive oil for 5 days
- 2nd day of treatment improvement in subjective complaints
- 5th day of treatment, all patients were free of complaints
(Schönbauer, Metka, & Salzer, 1983)

Indication Research Summary Table

Indication	Evidence Source	Dosage Information	Type of Evidence	Safety		Efficacy	
				Yes	No	Yes	No
Diabetic foot ulcers	(Martinez-Sanchez et al., 2005)	10 mg ozone at 50mg/l by rectal insufflation (20 sessions) Topical treatment (by bag) 60mg/l for 1 hour Lesion covered after with ozonated sunflower oil daily daily	Phase 2 Randomized Control trial	Yes		Yes	
Retinitis Pigmentosa	(Copello, Eguía, Menéndez, & Menéndez, 2003)	10 mg ozone in 200ml of gas mixture by rectal administration, 15 sessions	Phase 2 Double blind control trial	Yes		Yes	
Hepatitis C	(Zaky et al., 2011)	25-60% concentration mixed with 125 mL blood and reinfused,	Phase 2 Prospective case control study	Yes		Yes	

		rectal in sufflation 40% concentration, 300mL, 10 mL of 20 μg/mL ozone mixed with 3-5 mL of patients blood and injected IM.					
Degenerative Spine Disease	(Bonetti, Fontana, Martinelli, & Andreula, 2011)	CT guided oxygen/ozone intraforaminal injection followed by 4 weekly paralumbar injections	Phase 2 Prospective Study	Yes		Yes	
Anti-microbial action	(Schulz, Rodriguez, Mutters, Menendez, & Bette, 2003)	10 μg O3/mL concentration at 80 mL/kg volume daily injections into right lower abdomen of rats for 5 days	Animal studies	Yes		Yes	
Nephrotoxicity induced by ciplatin	(González et al., 2004)	Dose:1.1mg/kg conc: of 30 μg/ml By rectal insufflation once daily for 5 days	Animal studies (rats)	Yes		Yes	
Liver protection from injury due to ischemia-reperfusion	(Peralta et al., 1999)	Dose 1mg/kg 10 treatments, I per day 5-5.5ml at conc of 50μg/ml	Animal studies (rats)	Yes		yes	
Extracorporeal ozonation of blood	(Bocci et al., 1999a)	Safe and effective concentration ozone10μg/ml saline or blood through a gas exchanger	In vitro and in vivo animal studies	Yes		Yes	

Interferon induction (useful for viral diseases)	(Bocci & Paulesu, 1990)	Safe and effective concentration 42μg/ml ozone Human blood insufflated for 30 s with gas	In vitro human blood	Yes		Yes	
Tumor necrosis factor induction (immunomodulatory: helpful in viral diseases, immunodepressed patients, and tumor bearing patients)	(Paulesu, Luzzi, & Bocci, 1991)	Safe and effective concentrations 30 and 54 μ/ml ozone insufflated into human blood for 30 s	In vitro Human blood	Yes		Yes	
Immunological marker activation	(Bocci, Luzzi, Corradeschi, & Paulesu, 1994)	200 ml of ozone/oxygen gas mixture mixed with 250 ml blood (conc 54 μg ozone/ml of blood) with 5% of blood mass reinfused	Human blood	Yes		Mild effects	
Cerebral Circulatory Disorders	(Wasser, 1995)	Daily MAH treatments using 3000μg ozone	Phase 2	Yes		yes	
Proctitis and colitis	(Knoch & Klug, 1990)	Rectal insufflation of 300 ml oxygen ozone mixture at concentration of 20 μg /ml 2x per week	Phase 2	yes		yes	
Peripheral arterial circulatory disorders	(Rokitansky, 1982) (Mattassi, 1981)	Intraarterial injections of ozone into femoral artery, not done this way anymore but was effective. Now they do MAH 2000-	Clinical cases	Yes		Yes	

		4000 μg/treatment					
Vaginal Candidiasis	(Schönbauer et al., 1983)	Ozonated olive oil was applied for 5 days	Clinical cases	Yes		Yes	

Pharmacokinetics:

- It is essential to realize that ozone induces changes in the body, it is these changes that create the activity
- Ozone can not be measured directly in the blood because since it is a gas that is being mixed with blood, the ozone dissolves in the plasma and is therefore immediately dissipated
- Ozone itself is not the active ingredient specifically, it is the body's response to ozone that create the activity
- The pharmacokinetics of ozone must be viewed in light of gas solubility
- According to Henry's law ozone as any other gas, in pure water in relation to the temperature, pressure and ozone concentration

> *At a constant temperature, the amount of a given gas that dissolves in a given type and volume of liquid is directly proportional to the* partial pressure *of that gas in equilibrium with that liquid.*

- Ozone reacts immediately as soon as it is dissolved in biological water (physiological saline, plasma, lymph, urine)
- O_3 used in medicine is produced from pure medical oxygen via silent electrical discharge; it is not possible to use oxygen concentrators or oxygen/air mixtures due to their nitrogen component and the consequent possibility of nitrogen oxides being formed in the discharge tube
- Ozone has a half life 55 minutes in a 50 ml disposable injection syringe
- In the gaseous state (t ½ = 55 minutes in a 50 ml disposable syringe), ozone breaks down into molecular oxygen with system-dependent half life (2 O_3/ 3 O_2) or, in an aqueous medium, half life (t ½ = 10 h at 20 °C [68 °F] in
bidistilled water).
- The figure below explains the dissociation curves for ozone in ozone/pure oxygen gas mixtures in a 50mL glass syringe at different temperature and at constant pressure (101.35kPa)

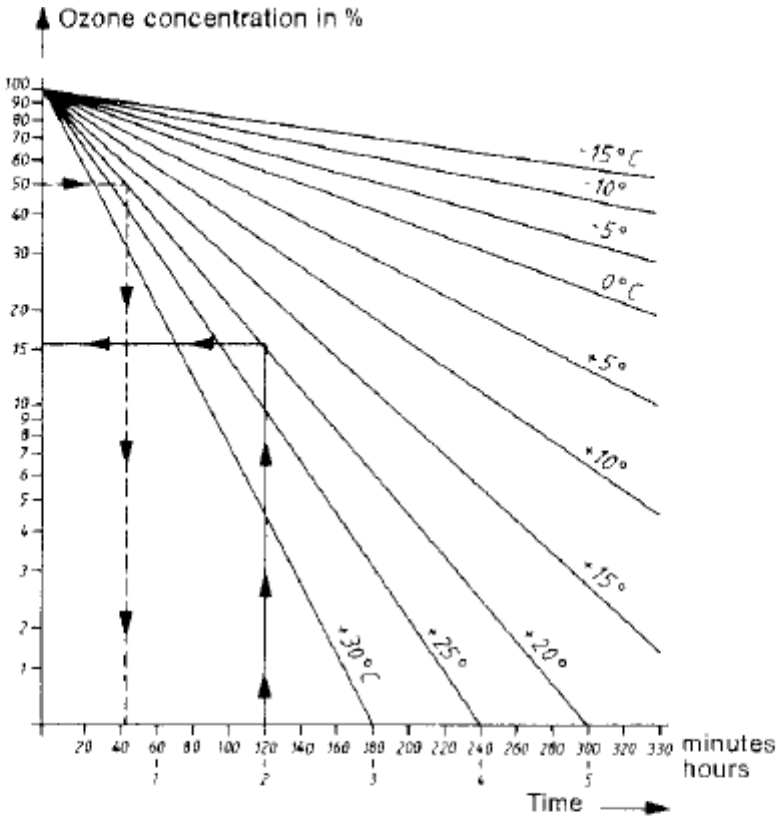


Fig. 35: Ozone distintegration periods in a glass syringe according to temperature

Example: a) At a temperature of 20 C/68 F, the ozone concentration drops to approx. 16% of its initial value after 120 minutes.

or b) The half-life period (the time after which only 50% of the original quantity of a substance is still present, the rest having disintegrated) is approximately 45 minutes at 20 C. (See also under half-life period.)

At low temperatures, the disintegration rate is slowed down, at high temperatures it increases correspondingly.

- In blood, it dissolves in plasma and instantly decomposes in a cascade of reactive oxygen species (ROS), including hydrogen peroxide (H_2O_2), superoxide anion (O_2^-), hydroxyl radical ($HO^\cdot$) and hypochlorous acid (HClO).
- Although the implication of this may sound counter intuitive, further explanation of how this reaction may be beneficial to health will be further explained in the pharmacology section, this is briefly outlined here to explain how the pharmacokinetics of ozone is to be measured. Again reiterating in the opening explanation, since ozone is a gas the kinetics of this gas will follow Henry's law of gas solubility, however in order to measure the pharmacokinetics of ozone in the body biomarkers resulting from the decomposition can be measured as seen in table below.
- The purpose of the studies performed were mainly to determine, the optimal concentration for treatment

- The ROS are normally produced during several processes of physiological relevance such as cell respiration by mitochondria, the respiratory burst that accompanies phagocytosis and xenobiotic detoxification, being also important cell messengers and gene transcription regulators
- Most of the ozone dose that comes into contact with blood is partly reduced by water-soluble antioxidants and partly transformed into ROS including lipid peroxides and other bioactive molecules, which are also checked by the antioxidant and scavenger systems

Table 1. Some biomarkers used to characterize the response to the *in vitro* exposure of human blood components or cell cultures to oxygen–ozone mixtures

Parameter	Biological sample/experimental setting	Effect	Type of response
TAS	Plasma[a,c]	↓	Time and concentration dependent
	Whole blood[a,c]	↔ (compensation by blood cells)	Time and concentration dependent
PTGs	Plasma[a,c]	↓	Time and concentration dependent
TBARs	Plasma[a,c]	↑	Time and concentration dependent
Haemolysis	Plasma (as free hemoglobin)[a,c]	↔ doses ≤ c ↑ doses ≥ d	Concentration dependent
MDA	Plasma[d]	↑	Concentration dependent
	RBC[d]	↔	/
α-Tocopherol	Plasma[d]	↓	Concentration dependent
	RBC[d]	↔	/
PDGF and TGF-1β	Platelet[a,c]	↑	/
TNF-α	Whole blood (a, b)	↑	Concentration dependent
INF-g	Whole blood (a, b)		Concentration dependent
IL-2	Whole blood (a, b)		/
IL-8	Whole blood (a, b)		Concentration dependent
NO_2 (iNOS activity)	HUVECs*[a,c]	↑	Concentration dependent

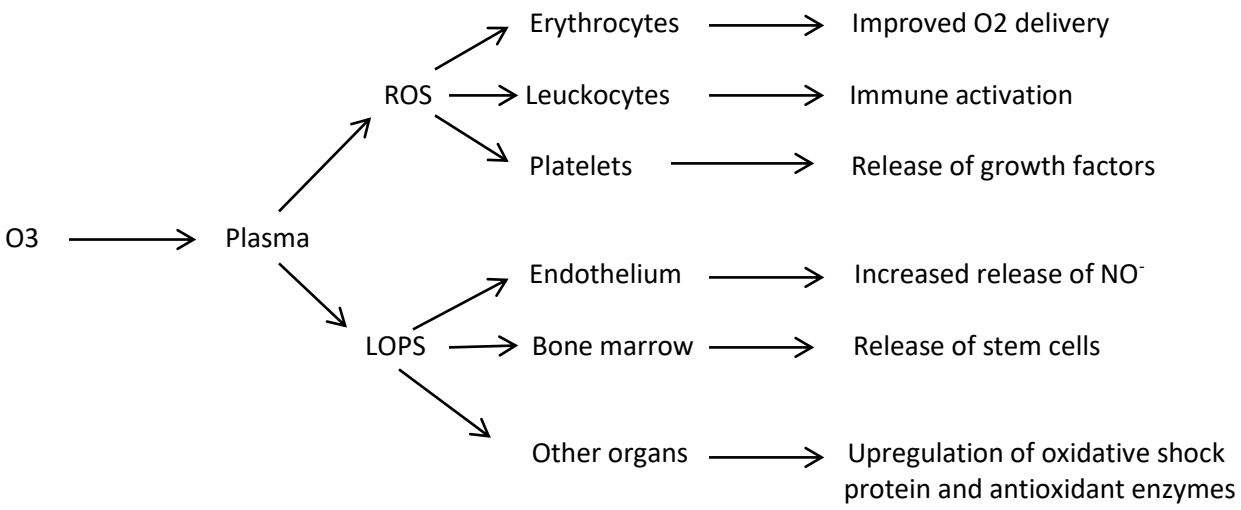
*Exposed to human serum treated with the doses of O_3 a and c and assessed for the formation of TBARs and H_2O_2 and the consumption of PTG.
O_3 doses used in these *in vitro* experiments were: [a]40 μg/ml; [b]70 μg/ml; [c]80 μg/ml; [d]100 μg/ml.
Experiments were performed over an incubation time of 1 min except in those cases in which time-dependence was evaluated (as specified in the column on the right).
Abbreviations: TAS, total antioxidant status; PTG, protein thiol groups; TBARs, thiobarbituric acid reactants; MDA, malonyldialdehyde, HUVECs, human umbilical vein endothelial cells.

(Beck et al., 1998; Bocci et al., 1998; Bocci et al., 1999a; Bocci, 2005; Bocci, 2006; Chang, 1986; Di Paolo et al., 2005)

- Ozone as any other gas, dissolves in the water, either of the plasma or into the extracellular fluids or into the thin layer of water covering the skin and the mucosa of the respiratory tract, gut, vagina etc.
- Ozone is a potent oxidant, reacting immediately w a number of molecules present in biological fluids such as antioxidants, proteins, carbohydrates and polyunsaturated fatty acids (PUFA)

- There are two fundamental processes involved in the action of ozone
  1. The initial reaction occurs in the plasma generating reactive oxygen species (ROS) as a as a byproduct, which triggers several biochemical pathways in blood (ie. In the glass bottle via autoheamotherapy). The ROS are further neutralized within 0.5-1 minute by the antioxidant system
  2. The second process occurs due to the interaction with lipids present in the plasma, lipid peroxidation. In the hydrophillic plasma environment, one mole of an unsaturated carbon double bond, such as arachidonic acid (PUFA) present in plasma triglycerides and chylomicrons, and one mole of ozone produces two moles of aldehydes and one mole of hydrogen peroxide (H_2O_2). This production of H_2O_2 and aldehydes derivatives known as lipid oxidation products (LOPs) are the products that are responsible for the biological and secondary therapeutic effects of ozone

- As soon as ozone dissolve in the plasma and reacts w/ PUFAs, the concentration of H_2O_2 increases but is rapidly diffused into the erythrocytes, leukocytes and platelets whereupon it triggers several biochemical pathways
- It is the lipid oxidation products (LOPs) formed during this process and reinfused back into the body that yields the second fundamental action
- The H_2O_2 acts as an intracellular signalling molecule, activating tyrosine kinase, which phosphorylates nuclear factor KB (NFKB), allowing the synthesis and release of cytokines
  - interferons (IFN-ß, IFN-γ)
  - interleukins (Type IL-1ß, 2, 4, 6, 8, 10)
  - tumour necrosis factor (TNF-α)
  - granulocyte-macrophage colony-stimulating factor (GM-CSF), and
  - growth factor (TGF-ß1)
- The H_2O_2 oxidizes cysteines and it will act on mononuclear cells, platelets, endothelial cells and erythrocytes
- The H_2O_2 entering into the erythrocytes are immediately reduced by GSH
  - GSH reductase utilizes the reduced nicotinamide adenine dinucelotide phosphate (NADPH) to recycle oxidized GSH (GSSG) to GSH
  - The oxidized NADP is reduced after the activation of the pentose phosphate pathway whereupon glucose-6-phosphate dehydrogenase (G6PD) is the key enzyme
- The reinfused erythrocytes enhance the delivery of oxygen into ischemic tissues due to a shift to the right of the oxygen haemoglobin dissociation curve due to an increase of 2,3 diphosphoglycerate (2,3-DPG), oxygen is not bonded so tightly, and is thus more easily released
- LOPs influence the erythroblastic lineage, allowing the generation of the cells w/ improved biochemical characteristics, with a higher content of 2,3-DPG and antioxidant enzymes, which are able to deliver more oxygen into ischemic tissue



O_3 conc. in blood [µg/ml]	IL-1 [pg/ml]	IL-2 [IU/ml]	GM-CSF [pg/ml]	IFN-ß [IU/ml]	IFN-γ [IU/ml]	IL-6 [pg/ml]
Control (sterile air)	80 (100%)	0.9	122	0	0.5	8
11	? [a]	?	?	?	1.5	20
25	?	?	?	?	1.0	28
42	145 (181%)	1.7	247	22	1.2	23
78	160 (200%)	1.8	283	30	2.1	35

[a] not measured

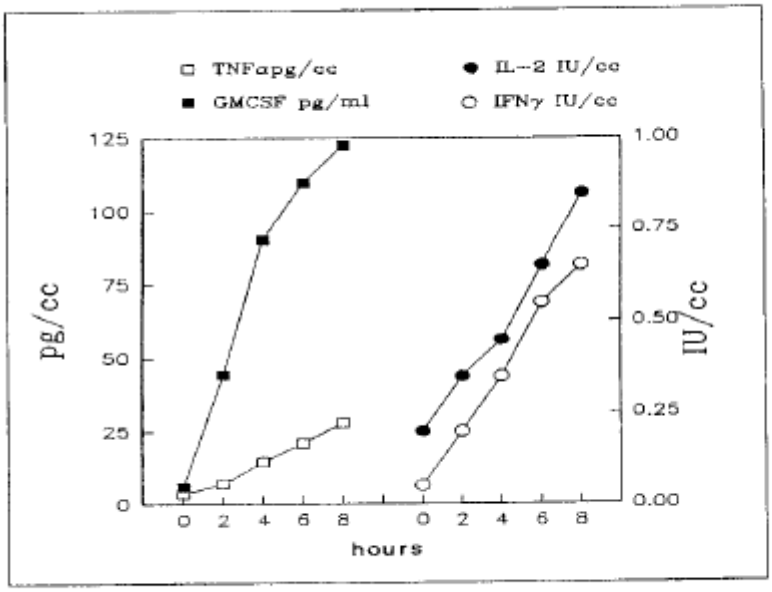


Figure 30
Ozone-produced physiological release of cytokins in whole blood (*Bocci*)

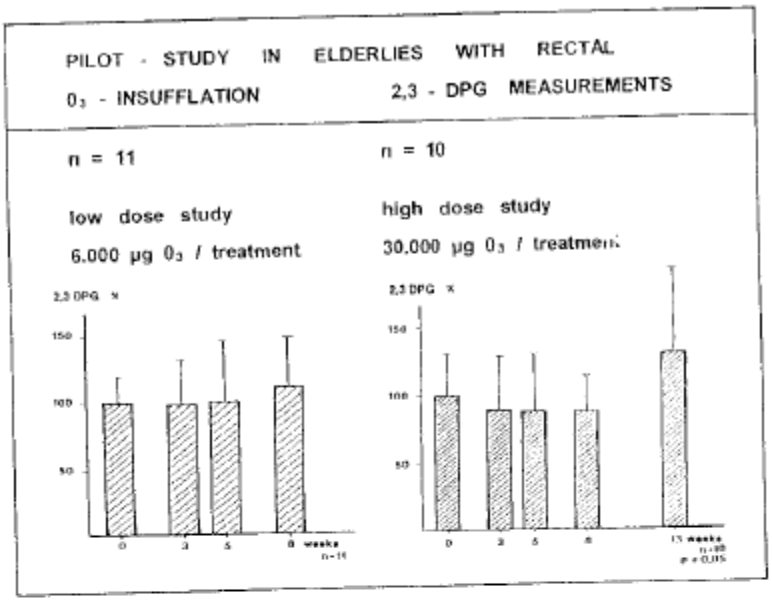


Figure 32
Pilot study in geriatrics (n = 10 or 11). Metabolic activation following rectal ozone application: 2,3-DPG values during the course of 10 irrigations, and 3 and 8 weeks after the end of treatment

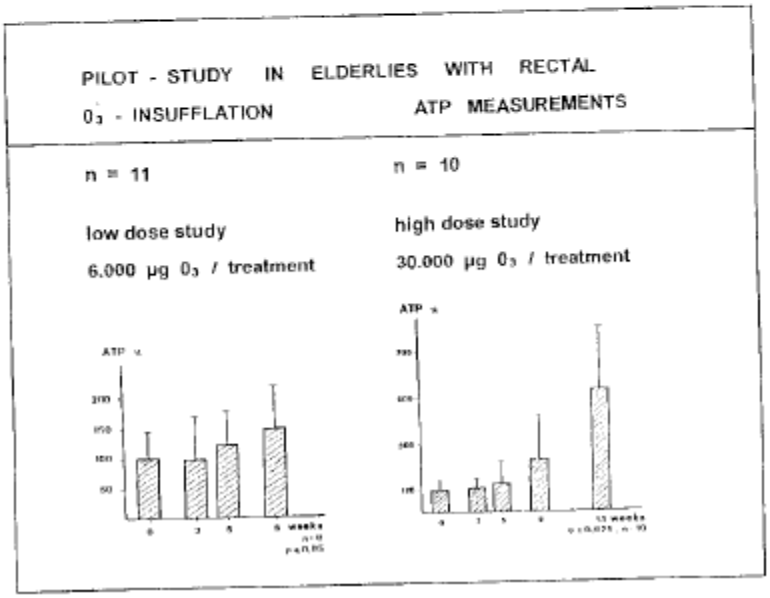


Figure 33
Pilot study in geriatrics (n = 10 or 11). Metabolic activation following rectal ozone application: ATP values during the course of 10 irrigations, and 3 and 8 weeks after the end of treatment

(Bocci, 2004)

Summary of biological effects

Erythrocytes

- These cells respond with an activation of glycolysis due to activation of the pentose phosphate pathway
- Increased adenosine triphosphate levels have been found (from 13899/260 to 19689/232 mM) in patients with age-related macular degeneration (ARMD) (atrophic form) after a therapeutic cycle (14 sessions) of autoheamotherapy
- Similar results also found in athletes and elderly patients after rectal insufflation
- An increase of 2,3-diphosphoglycerate level in oxyhemoglobin shifts to the right (p50 value increases); its dissociation curve implies an increased delivery of O2 into the hypoxic tissues.

- ROS have an extremely short life, LOPs, during the reinfusion of ozonated blood, return into the donor's circulation. While the LOPs are fairly stable in vitro, they are rapidly diluted from blood in vivo into body fluids, degradation by aldehyde dehydrogenases, excretion into bile and urine, and uptake in various organs including bone marrow cells
- During erythrogenesis, submicromolar LOP concentrations can upregulate the synthesis of antioxidant enzymes suggesting that ozone therapy enhances the generation of erythrocytes with improved metabolic characteristics

Leukocytes

- Ozone acts as an IFN-γ inducer and also as a weak (compared with mitogens) cytokine (such as tumor necrosis factor-α, interleukin-2, interleukin-6, interleukin-8, transforming growth factor-β [TGF-β]) inducer
- H_2O_2 is one of the most significant cytokine inducers. As already mentioned, after ozonation H_2O_2 freely diffuses into the leukocyte cytoplasm and activates specific protein kinases that, by phosphorylating I$\kappa\beta$ bound to the nuclear factor-$\kappa\beta$ allows the migration of the transcription heterodimer p50-p65 into the nucleus where it activates gene expression

Platelets

- It is known that ROS can induce platelet activation
- H_2O_2 and other ROS can activate phospholipase C, phospholipase A_2, cyclo-oxygenases and lipo-oxygenases
  and thromboxane synthetase, an increase of intracellular Ca^2+, release of prostaglandinE_2, prostaglandin $F_{2\alpha}$ and thromboxane A_2 with platelet aggregation

Endothelial cells and the vascular system

- During the reinfusion of ozonated blood, the endothelium comes in contact with traces of LOPs increasing the release of nitric oxide

Parenchymal cells in other organs

- Upon reinfusion of ozonated blood, LOPs can reach other organs such as the hypothalamus, endocrine
  glands, liver, kidneys and bone marrow.
- During prolonged treatment, cells throughout the body receive small and gradual pulses of LOPs that are responsible for: (1) neuro-endocrine responses, (2) the upregulation of antioxidant enzymes in several cell
  types and (3) inducing a number of stress or heat shock proteins (HSPs) such as HSP27, HO-1 (HSP 32), HSP72 and HSP90

Conclusion

- When human blood is exposed to a therapeutic dose of medical ozone, ozone reacts w/ substrates present in the plasma (PUFA, antioxidants etc..,)
- This reaction will yield ROS such as H_2O_2 immediate/initial phase and lipid oxidation products (LOPs) in the secondary/late phase
- The increase of H_2O_2 in the plasma will generate a concentration gradient whereupon it rapidly enters into the erythrocytes activating several biochemical processes and is simultaneously reduced to water by the intracellular antioxidant system (ie. GSH, catalase, GSH peroxidase)
- The LOPs are important for the secondary/late phase, which occurs when the ozonated blood is reinfused back into the blood stream
- The LOPs will upregulate antioxidant enzymes, oxidative stress proteins and release of stem cells
- The blood that is exposed to medical ozone undergoes a transitory oxidative stress which is necessary to activate the biochemical adaptive responses

(Beck et al., 1998; Bocci & Paulesu, 1990; Bocci et al., 1993; Bocci et al., 1994; Bocci et al., 1998; Bocci et al., 1999a; Bocci et al., 1999b; Bocci, 2004; Bocci, 2006; Bocci, Luzzi, Corradeschi, & Silvestri, 1994; Bocci, Luzzi, Corradeschi, Paulesu, & Di Stefano, 1993; Bocci, Valacchi, Corradeschi, & Fanetti, 1998; Di Paolo et al., 2005; Paulesu et al., 1991; Peralta et al., 1999; Valacchi & Bocci, 1999; Valacchi & Bocci, 2000; Viebahn-Haensler & Lee, 2002; Zimran, Wasser, Forman, Gelbart, & Beutler, 2000)

Contraindications and Precautions:

Contraindications

(Beck & Viebahn-Hänsler, 1995; Bocci et al., 1999a; Di Paolo et al., 2005; Viebahn-Haensler & Lee, 2002)

- Overall ozone therapy is a safe modality and hence little contraindications, the most obvious G6PD deficiency, whereas hyperthyroid and pregnancy is a precaution
    - Glucose-6-phosphate dehydrogenase deficiency
        - The H_2O_2 entering into the erythrocytes are immediately reduced by GSH
            - GSH reductase utilizes the reduced nicotinamide adenine dinucelotide phosphate (NADPH) to recycle oxidized GSH (GSSG) to GSH
            - The oxidized NADP is reduced after the activation of the pentose phosphate pathway whereupon glucose-6-phosphate dehydrogenase (G6PD) is the key enzyme
- Thus a deficiency of G6PD will create a haemolytic response
- Patients on ACE inhibitors
    - A slow infusion is required
    - A rapid reinfusion of ozonated blood created marked hypotension in these patients
- Hyperthyroidism
- Pregnancy
- Inhalation of ozone is prohibited
    - Medical ozone is generated by ozone and pure medical grade oxygen, however if ozone gets in contact with outside air, the contaminants in the air can become an irritant to the respiratory system and since the respiratory system have little antioxidant systems as compared to plasma thus it is imperative to reduce exposure
    - The World Health Organization permits an 8hrs work shift with an ozone concentration of 0.12µg/L
    - The maximum worksite allowable concentration is 0.2µg/L over 1hr
    - The odour perception to ozone is 0.02µg/L
- Ozone dosage and hemolysis
    - Ozone dosage measuring 10-40µg/mL for 50-100mL blood is the recommended dosage giving a quantity of 500-4000µg of ozone
    - Concentrations above 80µg/mL of ozone treated blood
        - Increases hemolysis, up to 10% at 100µg/mL
        - Decreases 2,3-DPG
        - Reduces activation of immunocompetent cells

Interactions:

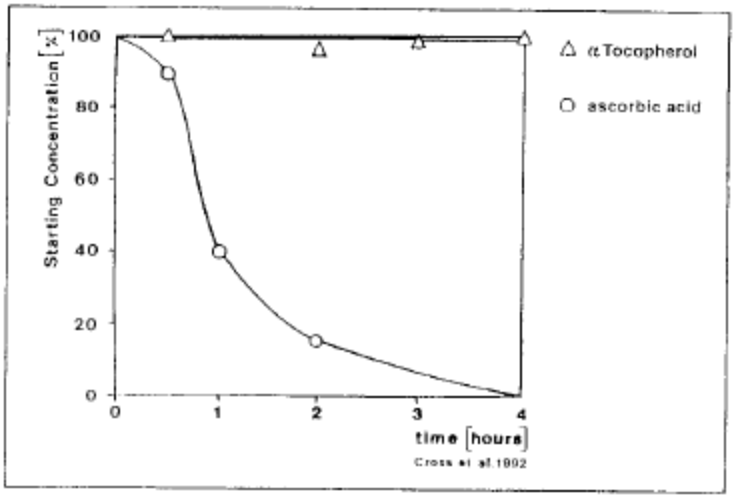
Ozone A New Medical Drug (Bocci, 2005)

- The only interactions with a pharmaceutical has been with ACE inhibitors
  - One mechanism of ACE inhibitors is an increase of bradykinins, a potent vasodilator and a rapid infusion of ozone treated blood can augment this action and thus create substantial hypotension
  - In order to circumvent this response with patients taking ACE inhibitors, slowing down the infusion is critical, since bradykinins are degraded in the plasma, by slowing down the infusion, this allows the breakdown of the bradykinins and thus reducing severe hypotension, this has been determined through 2 case studies

(Bocci et al., 1993; Viebahn-Haensler & Lee, 2002)

- High ascorbic acid plasma levels reduces the effects of ozone therapy
- Cytokine induction by ozone is suppressed by high plasma ascorbic acid

Figure 41



The effect of ozone on the antioxidants vitamin E (α-tocopherol) and vitamin C (ascorbic acid) in blood plasma according to Cross et al. (1992). The plasma was exposed to a continuous ozone concentration of 16 ppm, corresponding to 32 mg/m³, and the effects measured over a period of four hours.
Whereas vitamin C is increasingly oxidized by ozone, vitamin E shows practically no reaction at all; even after four hours, the initial value of vitamin E is still found

Adverse Reactions:

- If the appropriate settings of ozone dosage is adhered to (10-40µg/mL for 50-100mL blood) and a thorough case history taken (G6PD testing, pregnancy…) then the adverse reactions to the actual therapy is nil, aside from the anxiety by the patient in regards to any intravenous therapy
- Again, the only adverse reaction to occur would be if there is a prolonged and continuous respiratory exposure
    - However this is nullified, if the practioner has a medical ozone generator, which will reconvert the unused ozone back to oxygen
    - The methods for the production of medical ozone, prevents any release of ozone to the outside air

(Bocci, 2005; Viebahn-Haensler & Lee, 2002)

Search String Table

Database	Search term	# of Hits	Relevant Citation	Adverse Event	Likely/Unlikely
PubMed	adverse events for ozone therapy/medical ozone/oxygen-ozone therapy	1	Am J Forensic Med Pathol. 2000 Jun;21(2):144-7	Death	Unlikely,(not due to ozone directly but due to a rapid infusion and creating a gas embolism)

Antidote/Preventive Treatment:

(Bocci, 2005) page 8

- The most important preventative treatment for various adverse reactions is dependent upon the clinician
    - A thorough case history must be taken, to rule out the various contraindications (hyperthyroidism, pregnancy ,G6PD testing, etc…)
    - Ozone therapy is an option that should be available to a trained and qualified naturopathic doctor, however it is not the only therapy, the clinician must take into account all the available options
    - The most important preventative measure is to ensure the appropriate dosage (10-40µg/mL), this dosage can be easily obtained by a medical ozone generator which if the practitioner endeavours to use ozone therapy must purchase and maintain
    - The ozone generator will have a method for reconverting the unused ozone back to oxygen (ozone destruct unit)
    - Only ozone appropriate equipment must be used

- If all of the above measures are maintained then any and all adverse reactions can be nullified, however if a patient does complain of some respiratory discomfort due to some exposure during treatment the appropriate antidote should utilize IV ascorbic acid anywhere from 10-20g, a simple Meyer's cocktail, along with oral administration of NAC
    - Since high plasma ascorbic acid reduces the ozone effects

Toxicity and Treatment:
Review both toxic effects and LD50 data for the substance. Propose methods to prevent these toxic effects either with dose modification on patient surveillance. Outline the specific treatment and diagnostic steps that will antidote toxic effects.

(Bocci, 2005) page 8
(Viebahn-Haensler & Lee, 2002) page 137

- To restate, the biggest toxicity for ozone therapy is the dosage of administration
- This dosage should be between 10-40µg/mL treatment for 50-100mL of blood
- Dosages above 80µg/mL
    - Increases hemolysis, up to 10% at 100µg/mL
    - Decreases 2,3-DPG
    - Reduces activation of immunocompetent cells
- The other caution that must be taken into consideration is inhalation of the ozone, however if the practitioner has a medical ozone generator, this is circumvented by the built in ozone recycling mechanism
    - The World Health Organization permits an 8hrs work shift with an ozone concentration of 0.12µg/L
    - The maximum worksite allowable concentration is 0.2µg/L over 1hr
    - The odour perception to ozone is 0.02µg/L
- Brief exposure to inhaled ozone, if causes any respiratory discomfort can be antidoted with IV ascorbic acid, a Meyer's cocktail with ascorbic acid can be easily administered along with oral supplementation of NAC

Applicant Contact Information:

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L2R 7L9

(905) 684-4934

registration # 1212

Generic or Scientific Name:

In this section provide the chemical or scientific binomial name of the substance

Ozone, trioxygen, O_3

Manufacturer (If Applicable):

Ozone has an extremely short half-life (55 min) and so it has to be made on-site as needed.

Specialized equipment is required to do this. Medical grade oxygen and an ozone generator are required.

examples of where you can get an ozone generator

1. Longevity Resources

Sidney, BC, Canada, 1-877-543-3393, info@ozonegenerator.com

2. Ozonosan

Dr. J. Hänsler GmbH

Nordring 8 D - 76473 Iffezheim (Germany) Phone +49 (0)7229-30 460, fax +49 (0)7229-30 46 30, info@ozonosan.de

Storage Requirements:

Ozone has an extremely short half-life and reacts with many materials. So it has to made on site with specialized equipment as stated above and administered with certain non-reactive materials. Non-reactive materials include: glass, ceramics, specially anodized aluminum, V4A-quality stainless steel, polyethylene, polypropylene, and Teflon, other plastics must be silicon coated. The reinfusion apparatus for MAH should be made of glass. (Beck et al., 1998)

Both companies above carry various ozone resistant components to make and administer ozone.

Current Canadian Regulatory Status:

The National Association of Pharmacy Regulatory Authorities (“NAPRA”) is a voluntary association of provincial and territorial pharmacy regulatory bodies for pharmacies in Canada. Within the province of Ontario, NAPRA scheduling has been adopted as the classification schedule for substances. In this section indicate which schedule applies to this substance.

NAPRA Schedule	I ☐	II ☐	III ☐	Unlisted X☐

Summary of International Regulatory Status

Jurisdiction	Regulatory Status	Dosage Form Approved	Date of Initial Regulation
British Columbia	Approved by CNPBC with postgraduate certification	10-40 μg ozone/mL of blood	1993
Alberta	Approved by Alberta Association of Naturopathic practitioners	10-40 μg ozone/mL of blood	Before 2004

Manitoba	Approved by Manitoba Naturopathic Association	10-40 μg ozone/mL of blood	2010
Oregon, Washington, Arizona, Alaska, Colorado, Georgia, Minnesota, New York, New Jersey, North Carolina, South Carolina, Ohio, Oklahoma		10-40 μg ozone/mL of blood	
Mexico		10-40 μg ozone/mL of blood	

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Provide a ***complete*** bibliography of all sources, including those referenced specifically in other areas of the application.

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