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revisión

Ozone Therapy for Patient poisoned by Carbon Monoxide

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Keywords

Ozone Therapy

Carbon monoxide

Abstract

Carbon monoxide (CO) is a chemical produced from the incomplete combustion of natural gas or other products containing carbon. It is colorless, odorless and tasteless gas. Carbon Monoxide binds strongly to hemoglobin with higher affinity than Oxygen, affecting the Oxygen transport in the cells and deteriorating mitochondrial function. Nowadays, treatment is a high-flow Oxygen administration, moving CO out of the haemoglobin. The Ozone Therapy is one of the most important discoveries in the lasts years in the field of medicine as a therapeutic agent, being a technique with a high effectiveness, low cost and very practical. The aim of this project is to prove the effectiveness of the Ozone Therapy as a treatment in the carbon monoxide poisoning patients. Literature review has been carried out during the months of February and May of 2013 as well as updates the recent findings. The sources of this review were different databases such as: Google Academic, Scielo, Elvisier, Dialnet and Pubmed, with the collaboration of Dr. Gabriel Ruiz Garcia, Doctor who uses Ozone Therapy (Major Auto hemotherapy) in his private clinic, located in Aguilar de Campoo (Palencia). The Carbon Monoxide poisoning alters the physiological balance between oxidative stress and antioxidant defenses, favoring the formation of free radicals. In the situation of oxidative Stress Ozone, causes stimulation of the systems enzymatic antioxidants against the attack. All of the properties that confer to ozone molecule explain its direct reaction with the Carbon Monoxide molecule and its elimination from the organism. The applicability of Ozone Therapy for patient poisoned by monoxide carbon would provide a fast and simple treatment, preventing the appearance of delayed neurological sequelae, stimulates the production of cellular energy, maintains an oxygenated environment and activates the metabolism and the antioxidant cell mechanism

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1. INTRODUCTION

The carbon monoxide (CO) is a chemical produced from the incomplete combustion of natural gas or other products containing carbon [4 5]. The main cause of this type of poisoning occurs in properties with a little or no ventilation where there is an incomplete combustion of fuels or combustibles that we use for heating or for cooking such as natural gas, butane, petrol, wood or charcoal, exposure to gas combustion engines, inhalation of smoke from fires and industrial accidents. [2, 3, 41].

It is a colorless gas, odorless and non-irritating for the airways. Due to its physical and chemical characteristics and its capacity toxic has been called the silent invisible killer [2, 6, 11].

It is necessary a correct assessment of the carbon monoxide poisoning people due to its under-diagnosed and the clinical manifestations are nonspecific with absence of signs and symptoms, as well as carry out a correct treatment and subsequent control [1, 2, 5].

The CO inhaled is spreading rapidly through the alveolar membranes to be combined with the hemoglobin and the cytochrome c oxidase, affecting the transport of oxygen and deteriorating mitochondrial function [7, 24, 25].

Once in the blood, the CO binds strongly to the hemoglobin, whose affinity is 200-240 times greater than for oxygen, forming carboxyhemoglobin 1, 39, 41. This situation leads to a decrease of the transport of oxygen to the tissues, as well as there is a deviation of the dissociation curve of the hemoglobin to the left, so the little oxygen transported by hemoglobin is transferred to tissue with greater difficulty resulting tissue hypoxia, which is the responsible for the greater part of the acute symptomatology in the poisoning by carbon monoxide [5, 7, 8].
The clinical manifestations depend on the characteristics of the exposure (concentration of CO in the environment and time of exposure to the gas) and the affected person. The most frequent neurological symptoms are: headache, dizziness, weakness, ataxia, irritability, sleepiness, and, in severe cases, seizures and coma. After weeks or months after recovering from a serious poisoning, you may have the delayed neurologic sequelae characterized with disorders of the higher functions (apraxia, Agnosia, aphasia, memory faults, confusion, and personality disorders). [1, 2, 39, 40].

The correct identification of the symptomatology in a carbon monoxide poisoning and the subsequent action guidelines are essential for proper attention and to avoid the complications described. In addition to this, it is necessary to sensitize the population to perform a good prevention of toxicity by CO starting with a good management of the gas heaters, stoves, ovens etc., making periodic reviews of the combustion systems at home, maintain adequate ventilation and prevent the inhalation of the engines combustion products or vehicles in garages and enclosed spaces [9].

Today the treatment consists in the administration high-flow oxygen however there is a controversial issue in order to administer under normobaric or hyperbaric conditions [2, 39, 40].
On the other hand, there is a cyanide poisoning, which is produced by the combustion of many natural polymers (silk, wool) or synthetic (polyurethane, polyamide) containing nitrogen. The cyanide also produces an inhibition of the enzyme systems causing a tissue hypoxia [38].

Poisonings by cyanide has an antidote whose name is hydroxocobalamin or vitamin B12, which has some criteria for its administration [38]. These are:

Patient who has inhaled smoke from fire (traces of soot in the mouth, pharynx or sputum) and has neurological alterations (confusion, coma, agitation, convulsions) and also presents some of the following circumstances:

- ✓ Bradipnea (<12 rpm or respiratory shutdown/cardiorespiratory).
- ✓ Shock or hypotension or
- ✓ Lactate ≥ 8mmol/l or lactic acidosis.
- ✓

The maximum effectiveness has been seen in patients who have inhaled smoke from fires, are in a coma and have hypotension [38].

The present review focuses on the use of Ozone Therapy as a treatment for patient poisoned by carbon monoxide, which is another door that opens an alternative as a safe treatment and low cost. The ozone therapy is one of the most important discoveries during the last years in the field of medicine as a therapeutic agent. It is a natural therapy consisting of the application of a mixture of oxygen (95%) and ozone (5%), characterized by the simplicity of its application, its great effectiveness, low cost and very practical[10].

In 1785, the Dutch physicist Martin Van Marum, was the first to mention about the ozone during various experiments in which he discovered that by passing an electric spark through the air appeared a gaseous substance of characteristic odor, which had strong oxidizing properties but it was not until May 1840 when the German chemist Cristian Friedrich Schonbein synthesize it [12].

In 1857 was constructed the first technical ozonization device, created by Werner von Siemens with the help of a modern magnetic induction pipe, which was used in an installation for the purification of drinking water. Since then the ozonation allows you to obtain drinking water hygienically pure and suitable for human consumption. It was in the year 1893 when was installed in the Netherlands the first ozone water treatment system [12].

Later in 1885 was published the book "Ozone" written by Dr. Charles J.Kenworth, where details were given on the use of Ozone for therapeutic purposes [12].

There are references to the use of ozone during the First World War (1914-1918) by Dr. Albert Wolff of Berlin who encouraged the use of ozone for the wounds treatment [12].

The first ozone generator was patented by Dr Joachim Haensler in the year 1957, in Germany. The Swiss dentist Fish, sensed the enormous advantages of ozone in local treatment, who treated with good results to Dr Edwin Payr who immediately understood the usefulness of ozone was enthusiastic about its application in general surgery [12].

Nowadays many doctors in the world use ozone in their daily work obtaining good results. However the widespread application of the ozone therapy and its regulation by the authorities is a critical issue at the present time. In addition to the existing competition with the pharmaceutical industry which probably decreased the sale of drugs.

The majority of scientific work environment to ozone are related to toxic effects and their environmental impact. However, the studies on its mechanisms of action on the biological level have been increasing in recent years [12].

There is a lack of financial support which is required to carry out scientific research. There are a large number of books and research papers that constitute scientific support for the Ozone Therapy[12] and today this therapy is increasingly used in different countries of the world [42 43].

The Madrid Declaration on Ozone Therapy, is a reference document which includes an important annex on the "Therapeutic Windows for the use of ozone", in which appear the therapeutic foundations, the basic principles, the main routes of administration, the most appropriate pathologies and the general bases of treatment to be treated with Ozone Therapy and constitutes the summary of the scientific research of various countries and the result of many years of experimental and clinical practice. The Declaration was adopted at the International Encounter of Schools of Ozone Therapy, organized by AEPROMO (Spanish Association of Medical Professionals in ozone therapy), in the National Royal Academy of Medicine in Madrid (3 and 4 July 2010) [13].

In this document are the three basic principles to be taken into account before initiating any procedure ozone therapy. The basic principles are:

-Primum non nocere: Above all do no harm.
-Stagger the dose: In general, always start with low doses and increasing slowly, except in ulcers or infected wounds, which will conversely (start with high concentrations, and decreasing depending on the improvement).
-Apply the necessary concentration: higher concentrations of ozone are not necessarily best, the same occurs in medicine with all drugs.

1.1 Justification and purposes

The CO or the so-called "silent invisible killer"[2, 5, 11], has a large impact on human health, due to the fact that it is an under-diagnosed disease in the Emergency Services of many hospitals.

It is important the correct identification of the symptomatology of the Carbon Monoxide Poisoning, as well as the proceedings subsequent to perform an adequate attention avoiding complications, constitute the most important prevention and therefore, make the population aware to carry out a periodic review of its combustion systems at home and its annual cleaning, maintaining adequate ventilation.

The treatment includes removing the patient from the source of exposure and the administration of 100% oxygen until the normal levels of COHb[1, 2, 5].

This review intends to explain the use of ozone intravenous (Major Auto Hemotherapy) as treatment in patient poisoned by Carbon Monoxide through the actions of ozone in the body with the literature review consulted getting dissociating the CO of the Hemoglobin. It is a simple and economic technique, becoming in the patient poisoned by CO in a treatment with a number of benefits for its elimination, prevention of further complications and low economic cost.

1.2 Limitations of the study

Unfortunately this review has the following limitations:

- Do not dispose of any case during the months of study in the consultation of Dr. Gabriel Ruiz Garcia and therefore the results are based on the physiology studies and the researches carried out over the years about the action of ozone in the organism.
-There is no study on the use of ozone as treatment in patient poisoned by carbon monoxide.
-and therefore do not have a laboratory to prove the study.

2. **Objectives**

2.1 Main objective:

2.1.1 Prove the effectiveness of the Ozone Intravenous (Major Hemotherapy) as a treatment in patients poisoned by carbon monoxide.
2.2 Specific objectives:
2.2.1 Explain the importance of the cell, the components that the form and its functions.
2.2.2 Explain the influence of free radicals into the cell.
2.2.3 Assess and delve into the different mechanisms of action of ozone in the body.
2.2.4 Compare the present treatment used with the treatment with ozone in a patient intoxicated by carbon monoxide.

3 MATERIAL AND METHODS

3.1 Type of study

This study is based on a wide literature review during the months of February to May 2013 and its subsequent update until January 2016 of the following sections:
- Cellular Physiology.
- Radicals, reactive oxygen species, antioxidants.
- Carbon monoxide poisoning.
- Ozone and its mechanism of action.
Different documentary sources such as books on cellular physiology, as well as electronic data bases have been used. It also had the collaboration of Dr. Gabriel Ruiz Garcia, Graduate in Medicine and Surgery who uses Intravenous Ozone (Major Auto Hemotherapy) in his clinic, located in Aguilar de Campoo (Palencia, Spain).

3.2 Search strategy

The sources of this review were the following databases:
- Google Scholar.
- Scielo.
- Elsevier.
- Dialnet.
- PubMed.

And the following key words have been used:
-Carbon Monoxide poisoning.
-Ozone therapy.
-Oxidative stress.
-Antioxidants.
-Reactive Oxygen Species
-Free Radicals.

3.3 Description by chapters.

Describe the chapters of the bibliography consulted beginning with a brief summary of the Cellular Physiology, continuing with a description of the action of the radicals and the antioxidant systems of the organism. Finally the carbon monoxide poisoning and the Ozone as therapeutic agent will be describe.

4. Results

4.1 Chapter 1: The cell, the basic unit of our life. Cellular metabolism.

All living organisms are composed of cells. The cell is the morphological and functional unit of all living beings.

It is an essential part to know the cells operation and their components to be able to understand and explain the action of ozone therapy in the organism due to ozone acts at the cellular level by improving the energy efficiency of the cell.

Our Cells need oxygen to produce energy and to fulfill its functions but sometimes this oxygen can be harmful when there is an overproduction of their Reactive oxygen species and their natural enzymatic defensive systems are depressed[17]. There are studies on the damage to our cells due to factors such as age, stress, environmental pollution [20]…

In the aerobic organisms life that use oxygen as a means to achieve energy, there is the danger that its antioxidant defenses will be overwhelmed by the forces oxidants. This situation is called oxidative stress, which is explained in the next chapter.

The majority of the cells have three basic parts: the cell membrane, the cytoplasm and the nucleus. Each cell contains several mitochondria, which are located in the cytoplasm, are responsible for providing energy to the cell to carry out their functions[16].

The cells continuously exchange matter and energy with the environment in order to build and maintain internal structures and are able to perform their roles so that ensure their survival. These transformations occur through a set of chemical reactions catalyzed by enzymes that is called metabolism. In the metabolism cells convert the nutrients, usually rich in carbon compounds, in basic components through degradation or synthesis processes, called catabolism and anabolism, respectively [15].

The animals take food which is eaten in the form of carbohydrates, fats and proteins. These complex molecules are going to be transformed and absorbed into the intestine. The carbohydrates in the diet comes mainly from starch, which breaks down, forming glucose; fats are converted in fatty acids and glycerol, and proteins are broken down into its constituent amino acids. These degradation products are used by the body cells for the production of ATP, which is a good method of use of the chemical energy[14].

The ATP can be summed up in two ways: first, from the glucose degradation into pyruvate and secondly, from oxidative metabolism of pyruvate and acetate through the Krebs cycle[14].

In living systems, the glucose oxidation takes place in two main stages:
-The first is known as glycolysis which takes place in the cytoplasm of the cell.
-and the second stage is the breath, which consists of two stages: the Krebs cycle and the electron transport, occurring within the mitochondria.

During the glycolysis the glucose molecule of six carbon atoms is divided into two molecules of a compound called pyruvic acid (or pyruvate) In other words, a molecule of glucose is converted into two molecules of pyruvic acid. The result obtained is two molecules of ATP and two molecules of NADH by glucose molecule [16].

The two molecules of pyruvic acid still contain a large part of the energy that was stored into the original glucose molecule. The pyruvic acid can follow two ways: one is the aerobic (with oxygen) and the others are anaerobic (without oxygen). The aerobic way is the main route of energy metabolism of the majority of the cells and that, as its name indicates, occurs in the presence of oxygen[16].

In the absence of oxygen, the pyruvic acid can be converted into ethanol (ethyl alcohol) or in one of several different organic acids, of which the lactic acid is the most common[16].

In presence of oxygen, the next stage from the glucose degradation continues with the progressive oxidation of the pyruvic acid to CO2 and water, process known as respiration. The term respiration has two meanings in biology. One is the inspiration of O2 and the exhalation of CO2. And the other meaning of breathing is the food molecules oxidation using O2[16].

The cellular respiration takes place in two stages: the Krebs cycle and transport terminal of electrons. These reactions are developing within the mitochondria. In the mitochondria, the pyruvic acid derived from the glycolysis is oxidized to CO2 and water and, in this way, completes the glucose molecule degradation[16].

The pyruvic acid which is located in the cytoplasm, where occurs the glycolysis, is transported in a selective manner toward the mitochondrial matrix. Before entering in the Krebs cycle, the molecule of three carbons of the pyruvic acid is oxidized. The carbon and oxygen atoms from the carboxyl group are deleted in the form of CO2 and there is an acetyl group of two carbon left[16].

The original glucose molecule has oxidized into two molecules of CO2 and two acetyl groups and also has been formed four NADH molecules (two in the glycolysis and two in the oxidation of the pyruvic acid). Each acetyl group is accepted momentarily by a compound known as a coenzyme A (CoA). Like many other coenzymes, coenzyme A is a large molecule, part of which is a nucleotide and the other a vitamin. The combination of the acetyl group and the CoA is abbreviated acetyl-CoA. The formation of the acetyl-CoA is the nexus between the glycolysis and the Krebs cycle[16].

When entering the Krebs cycle, the acetyl group of two carbons is combined with a four carbons compound (Oxaloacetic acid) and produces a six carbons compound (citric acid). During this cycle, two of the six carbons of citric acid are oxidized to CO2 and regenerates the oxaloacetic acid and it end up forming a cycle[16].

The glucose molecule is already completely oxidized. Part of its energy is used in the transformation of ADP and phosphate in ATP. The largest amount of energy is in the electrons that are separated from the carbon atoms and were taken to the acceptor NAD and FAD, which were reduced to NADH and FADH2[16].

During the electrons terminal transport, that is the final stage of the breathing, these electrons of high energy are driven, step by step, to the lower energy level and are captured by the oxygen. This movement is possible due to the Electron transport chain, constituted by a series of electron acceptors, each able to accept electrons to an electronic level slightly lower than the precedent. Cytochromes are the main components of the electronic transport chain. Although the structures of the cytochromes are all similar, each differs enough to take electrons with different energy level[16].

In relation to the carbon monoxide poisoning, was proved the union of CO to the cytochrome A3 of the cytochrome c oxidase that is the last component (C-IV) 24 of the mitochondrial electron transport chain and therefore this alteration of the mitochondrial respiratory chain has a key role in this imbalance, in favor on the formation of free radicals [28].

When electrons are moved by the transport chain, jumping to lower energy levels, energy is released. This energy is quickly returned by the mitochondria and is used to synthesize ATP from ADP, is a process called oxidative phosphorylation. The quantitative measures show that for every two electrons that pass the NADH to oxygen, are formed three molecules of ATP from ADP and phosphate. For every two electrons that pass the FADH2 that are collected at an energy level somewhat lower, there are two molecules of ATP[16].

With the synthesis of ATP during oxidative phosphorylation, a process that began with the glucose molecule comes to an end.

The cells are the structural and functional units of all living organisms and constitute the essential part of our lives. The investigations of the ozone administration with adequate therapeutic doses are capable of forming discrete quantities of free radicals providing positive roles at the cellular level. The Ozone Therapy stimulates the energy production at cellular level, maintains an oxygenated environment and stimulates the metabolism and the antioxidant mechanism of the cell.

4.2 Chapter 2: Free radicals

From the biochemical point of view is considered oxidation to any process in which occurs electron lost, oxygen uptake or an assignment of hydrogen (dehydrogenation) and reduction in which are captured electrons or oxygen is lost. Any process of oxidation is always accompanied by another reduction. They are reactions reduction-oxidation or redox reactions between pairs conjugates[17].

In nature everything is almost oxidized by the oxygen. These reactions of reduction-oxidation are very important in biochemistry due to living beings obtain most of its energy from them[17].
In the aerobic metabolism, carried out by the eukaryotes and many prokaryotes, takes place a process that allows you to store the free energy produced in the oxidation of carbohydrates and other organic compounds, in the form of ATP. But this oxygen which is essential for life can also be a source of disease through an uncontrolled production of oxygen free radicals (OFR) which damage the macromolecules (lipids, proteins, carbohydrates and nucleic acids) and alter the cellular processes (functionality of the membranes, production of enzymes, cellular respiration, etc.)[17].

In the year 1956 Harman proposed the theory of free radicals in the aging, suggesting that the free radicals produced during the aerobic respiration cause oxidative damage which accumulates, and results in a gradual loss of the mechanisms homeostatic, in an interference of patterns of gene expression and the loss of the functional capacity of the cell, which leads to aging and death [18].

The mitochondria is considered the most important source of reactive oxygen species (ROS) [18] [19] at the level of the electron transport chain. The researchers say that the ROS generated may cause damage to both the internal membrane of mitochondria as to the components of the electron transport chain or the mitochondrial DNA, increasing more ROS production and consequently more damage to the mitochondria and an oxidative stress increase due to the production of oxidants[18].

There are also other sources of free radicals such as the peroxisome (organelles of cytoplasm very rich in oxidase) that generate H_2O_2, which is purified by specific enzymes (catalase) and transformed into water; polymorphonuclear leukocytes (when activated by several proteins that act on them). The leukocytes have in their membrane the enzyme NADPH oxidase generator of O_2 in the presence of iron is transformed in the highly toxic OH- (inflammatory processes). And finally another source is the enzyme xanthine deshidronasa, which are found in the endotelios[19].

Free radicals are atoms or groups of atoms that have one unpaired electron or free, being very reactive due to they tend to capture an electron of stable molecules in order to achieve its stability electrochemistry. Once the free radical has managed to steal the electron needed, the stable molecule becomes a free radical by being with an unpaired electron, thus initiating a true chain reaction which destroys our cells[20].

Free radicals are not intrinsically harmful; in fact, our own body produces them in moderate amounts to fight bacteria and virus. These actions occur constantly in the cells of the body, a process that must be controlled with an adequate antioxidant protection. An antioxidant is a substance capable of neutralizing the oxidative action of the free radicals through the release of electrons in our blood, those who are captured by the free radicals. The problem for the health occurs when the body has to bear an excess of free radicals during years, produced mainly by external contaminants, such as mainly atmospheric pollution and smoke from cigarettes, which produce different types of free radicals in our body. Equally certain foods in our diet contribute to an increase in RL, as are the consumption of hydrogenated vegetable oils such as margarine and the consumption of Trans fatty acids as the fats in the meat and milk[20].

An excess of RL disturbs the balance producing the so-called oxidative stress. Within the most important inorganic radicals are: the molecular oxygen O_2, the radical-superoxide anion (O_2 -), the hydroxyl radical (OH-) and its immediate precursor hydrogen peroxide (H_2O_2). The secondary or organic radicals are the radical peroxy (ROO-), the organic hydroperoxide (ROOH) and lipids peroxidados[17].

To combat and neutralize these RL there are defense systems, which are divided into two large groups: in the first place the antioxidant enzyme systems able to metabolize the RL generated in the cellular redox processes. These are the catalase of the peroxisome, glutathione peroxidase and superoxide dismutase[17].

And secondly, the non-enzymatic or exogenous (from the diet), among which we find the vitamin C or ascorbic acid and vitamin E or alpha tocopherol [17, 19, 20] that act by neutralizing the singlet oxygen and capturing hydroxyl free radicals19.

The functions of the enzyme systems that are present in the body of the living beings, protecting against the formation of new RL are the following [21]:

-Superoxide dimutasa (SOD) catalyzes the dismutación superoxide anion, causing hydrogen peroxide.
-Catalase (CAT) is a tetrameric enzyme that catalyzes the decomposition of hydrogen peroxide in water. It is present in most eukaryotic cells, located at the level of the peroxisome.
-Finally, is glutathione peroxidase (GPX) also contributes to the elimination of hydrogen peroxide, but unlike the CAT, which uses the hydrogen peroxide as giver of electrons, uses the reduced glutathione.

On the other hand, all the cells are surrounded by a membrane that separates them from the extracellular medium. The basic structure of all biological membranes is the lipid bilayer, which works as a barrier of selective permeability (Goodam, 1998). They are rich in polyunsaturated fatty acids (PUFAs) and therefore vulnerable to attack of free radicals which result in the lipid peroxidation. This is usually induced by a hydroxyl radical that subtracts a hydrogen to the lateral chain of a fatty acid forming a radical carbonated, which generates a string of oxidative reactions [20].

There are numerous pathologies that have been associated with an imbalance between oxidants and antioxidants. This damage to the biomolecules that determine the RL has been implicated in the genesis or exacerbation of numerous processes[19].

-Cardiovascular system: atherosclerosis, myocardial infarction, cardiac surgery, diabetes, heart disease, alcohol.
-Neurological system: Parkinson, Alzheimer, alcoholic neuropathy, hyperoxia, ischemia or cerebral infarction, head injuries.
-Ocular system: cataract, degenerative damage of the retina, retrolental fibroplasia.
-Respiratory System: respiratory distress, smoking, lung cancer, emphysema.
-SOMA: rheumatoid arthritis.
-Kidney: autoimmune syndrome, nephrotoxicity by metals.

These physiological alterations result from the oxidative stress, can be prevented with antioxidant defense mechanisms, mentioned above, both of enzymatic nature as non-enzymatic, and they are present both in the body itself as in the diet consumed.

This section has special importance to explain the mechanism of action of ozone in the body and its role in the oxidative stress, stimulating the enzyme systems antioxidants protectors against the action of the reactive species or metabolites of oxygen.

4.3 Chapter 3: Carbon Monoxide Poisoning

Carbon monoxide is a chemical produced from the incomplete combustion of natural gas or other products containing carbon[4] such as combustion of organic or inorganic material that contains carbon atoms and which is burned in conditions of relative lack of oxygen, giving rise to the formation of CO instead of carbon dioxide (CO_2). This phenomenon is observed in explosion engines and the heating devices and hot-water boilers installed in the housing. The smoke from the fires is rich in CO, but also in other gases such as cyanide which is as or more dangerous as the first[22].

The CO is a toxic gas, odorless and colorless, lighter than air and non-irritant[40]. Given by its inhalation is not perceptible some authors call it "the hidden enemy" or "winter killer" 6, 11.
The toxicity of CO essentially depends on the ability of this molecule to join the haem groups that contain some proteins. Their interaction with two of them is of key from the physiopathological point of view[2, 11].

The main physiopathological mechanisms of the CO poisoning are tissue hypoxia and the direct cell damage by:

-Carboxyhemoglobin formation (the affinity of CO by hemoglobin is 200-240 times greater than for oxygen, displacing it and causing hypoxia) [5, 39, 41]. In addition to this greater affinity, CO also produces a shift to the left of the oxygen dissociation curve with the Hb, with what the little oxygen that Hb transports has an assignment more difficult to reach the tissues[2].
-Connection to other proteins (such as the heart and muscle myoglobin altering muscle function, therefore, the myocardial dysfunction hypoxic originates bad infusion).
-and direct cell damage 5: the main factor to explain the deaths by CO and neurological sequelae characteristics by this poisoning is its inhibitory capacity, deep and sustained the complex IV of the mitochondrial electron transport chain and, therefore, its negative impact on the aerobic metabolism of mitochondria, especially in organs and tissues more dependent on oxygen, as the central nervous system[11].

This mitochondrial alteration had already been suspected from Haldane at the beginning of this century[23] and it was in 1939 when it was found for the first time in vitro the union of CO to the cytochrome A3 of the cytochrome c oxidase that is the last compound (C-IV) of the mitochondrial electron transport chain24. However, it was not until the year 1990 when it was found in vivo in animal models this union of CO to the cytochrome c oxidase mitochondrial[25].

This mitochondrial dysfunction also takes place in the human being[26] so in three intoxicated persons of acute form by CO, were able to objectify a marked inhibition (76%) of the activity of the cytochrome c oxidase of peripheral blood lymphocytes, and that this enzyme took 12 days to recover their basal values of activity, despite the fact that with HBO (Hyperbaric Oxygen) the concentration of carboxyhemoglobin was normalized in a few hours. At the same time, it is worth noting the persistence of some symptoms, especially neuromuscular (headache, nausea, weakness), during this whole period of time. In addition, in a subsequent study also have been able to observe how it increases the lipid peroxidation of the membranes of these lymphocytes[27], a fact that suggests that the acute intoxication by CO can alter the physiological balance that exists between oxidative stress and antioxidant defenses. In this sense, the alteration of the mitochondrial respiratory chain would have a key role in this imbalance, in favoring the formation of free radicals[28].

The symptoms of CO poisoning is very different, little specific and affects various systems, hence the difficulty in the diagnosis. Organs that require a high concentration of oxygen, such as the brain (body more sensitive to the inhalation by CO) and the heart, lose functionality easily by this poisoning. The most frequent neurological symptoms are: headache, dizziness, weakness, ataxia, irritability, sleepiness, and, in severe cases, seizures and coma. We must not forget the late neurological syndrome, in which the patients after recovering from a serious poisoning, after weeks or months presented new neurological symptoms[39]. With regard to the cardiovascular system, the most frequent symptoms is dyspnea, the heart is quickly affects and produce arrhythmias and ischemic changes. In the digestive tract occur frequently nausea, vomiting, diarrhea and abdominal pain. On the muscular system, weakness and muscle pain consequence of rhabdomyolysis produced by the CO[5].

Therefore, the organs with the highest demand of oxygen are the most susceptible to injury, and the brain and the cardiac effects dominate the acute clinical features and also for assessing the risk of late effects or permanent[40].

The symptoms will be different depending on the characteristics of the exposure (concentration of CO in the environment and time of exposure to the gas) and the affected person, evolving from a mild symptoms with headache, nausea, vomiting and dizziness, to which are added, when increases the exposure to toxic, drowsiness, irritability, tinnitus, to severe forms where you can produce syncope, seizures, hypotension, coma and death[5, 11].

The main treatment in patient poisoning by carbon monoxide is the administration of oxygen under normobaric or hyperbaric conditions depending on the case. The oxygen moves the CO of the COHb, which accelerates the elimination and decreases its arrival in the cell from the bloodstream. Likewise, dissociation power of CO with proteins (Hb, myoglobin, cytochromes) and decreases the production of free radicals. Given that the oxygen in normobaric conditions has no side effects, should be administered before any diagnostic suspicion, without waiting for the laboratory confirmation.

With regard to the administration of normobaric oxygen, it should be administered as soon as possible with high flow oxygen (100%), continuously and with mask reservoir. In severe cases, you must use the hyperbaric oxygen therapy. You have to think that the average life of the COHb is 4 to 6 h with O2 at 21%, decreases to 60-90 min at 100% O2 and with hyperbaric O2 to 2-3 atmospheres the average life of the COHb is 23 min[5].

The biological half-life of COHb is much less than the intracellular elimination of toxic and the neutralization of the oxidative damage caused.

The use of the hyperbaric oxygen therapy is controversial due to the lack of sufficient evidence of effectiveness on the hyperbaric oxygen therapy and it may worsen the late neurologic sequelae (Chiew A.L, Buckley N.TO, 2014)[39].

HBO could also increase the oxidative stress during recovery and is substantially more expensive than the normobaric oxygen. In addition the use of this therapy may be complicated by barotrauma, seizures, pulmonary edema, and claustrophobia[39].

Similarly, it has been investigated on the use of certain medications as a treatment to reduce the consequences of late neurological syndrome. Among them are the N-acetylcysteine antioxidant that restores the intracellular levels of glutathione and the ability of cells to resist the mechanisms of reactive oxygen species. As well as the steroidal anti-inflammatory and immune suppressors such as dexamethasone or methylprednisolone which could be used for severe inflammation in the CO poisoning [39, 40].

Therefore, it is now suggested different treatments in combination to achieve a good recovery of patients poisoned by carbon monoxide. The hyperbaric oxygen therapy has become controversial to only be accepted as optimal treatment standard in the carbon monoxide poisoning as well as the high cost involved in the use of this treatment.

4.4 Chapter 4: Ozone, mechanism of action in the body.

The air is a gaseous mixture composed of 78% nitrogen, 21% oxygen and 1 per cent of different compounds (such as argon, carbon dioxide and ozone)[29]. The ozone is the most important gas in the stratosphere, reaching their maximum concentration (above 1000 ug/m3) to a height of 20-30 km. It is a gas of an unstable nature, sky blue in color, 1.6 times denser and 10 times more soluble in water than oxygen and is the third most powerful oxidant after the fluoride and persulfate[12].

Ozone is produced from three basic sources of energy: chemical Electrolysis, electric shocks and UV light radiation. Due to the ozone is an unstable gas cannot be packed or stored, it must be used immediately because it has a half-life of 40 min at 20C [12].

The word ozone derives from the Greek word "ozein" that means having smell[10]. It has a typical characteristic phosphor odor in the air after an electrical storm intense or to the shore of the sea in the dusk of a hot and sunny day of summer. Its name is peroxide of oxygen and its chemical symbol is "O3". The O3 is always obtained from the molecular oxygen (O2), which by the action of electromagnetic forces produced naturally or artificially is literally divided into two atomic oxygen (O1), which are forced by these same forces to bind to other molecules of O2 being shaped and producing the molecules of O3. The O3 is an allotropic form of O2, unstable in normal conditions and easily becomes molecular oxygen: "O3 = O2 OR1" [30].

Between the biological effects of ozone emphasizes its antioxidant capacity.

Ozone reacts immediately when it is dissolved in the water biological (physiological serum, plasma, lymph and urine), acting the atomic oxygen as a radical highly reactive. Immediately, due to its high reactivity, ozone reacts with compounds such as antioxidants, carbohydrates, proteins, and polyunsaturated fatty acids (PUFA preferably), ascorbic acid and ureic compounds. In these reactions, organic peroxides, hydrogen peroxide (H2O2), ozone and aldehydes are generated, which in adequate quantities and controlled exercised by different biological actions that give to ozone a set of therapeutic properties[31]. This means that the dissolved ozone in the plasma water acts as a pro-drug generating chemical messengers which will accelerate the transfer of electrons and the overall metabolism[32].

During the last fifteen years, through the use of modern medical ozone generators, has been studied with precision the reactions of the ozone in human blood and is has clarified that the toxicity of ozone depends on your dose[32]. More specifically, in 1998 came the first ozone generators photometers able to accurately measure the ozone concentration and it was clarified how it works ozone when mixing blood ex vivo, due to that there was a lack of knowledge regarding the biochemical reactions of ozone in human blood[33].

Ozone is one of the most controversial gases because it is useful in the stratosphere to block UV radiation but toxic in the troposphere during air chronic inhalation. This is because in human beings the great extension of the alveolar surface (around 70 m2) is protected only by a low volume (approximately 25 mL) of fluid that, having a content of antioxidants small, cannot quench the activity strong oxidizer of ozone in the garrison[35].

Otherwise is for the blood, because the plasma and blood cells have a remarkable amount of antioxidants[34].

There are different reviews that demonstrate a comparative analysis of ozone between the lungs and the blood and this clarified the possibility of using the Ozone as therapeutic agent, always taking into account the dose used[34].

The numerous investigations on the ozone properties show their ability to react with the most organic and inorganic substances until its complete oxidation was established, as well as the influence of this gas on substances that have double and triple layers, among which are related proteins, amino acids and unsaturated fatty acids, forming part of the composition of the complex plasma lipoprotein and double layers of cellular membranes[12].

Due to the powerful antioxidant capacity of the blood due to its hydrophilic antioxidants, lipophilic and cellular enzymes, some of the dose of ozone dissolved in the water of the plasma are instantly neutralized by free antioxidants (mainly uric acid, ascorbic acid, reduced glutathione-AGG, cysteine and albumin), while the remaining ozone reacts with polyunsaturated fatty acids[34].

Thus, the potential energy of ozone is transferred finally in two messengers which are fundamental to H2O2 as a reactive oxygen species (ROS) and LOP (product of the lipoperoxidation)[35]. Therefore Ozone acts as a pro-drug because during these quick reactions ozone disappears but generates two crucial messengers[33].

Due to the reactivity of the ozone, these biochemical reactions occur in few seconds and in fact, within the five minutes in which you mix an average of 200 ml of human blood ex vivo in a sterile vial with the corresponding volume of 200 ml of the mixture of gases (O2 + O3), ozone is totally neutralized while approximately 95% oxygen dissolved in the water of the plasma, completely saturated hemoglobin (Bocci V, Traglabi V, Zanardi I, 2011).

The oxygenation of the blood rises to approximately 400 mm Hg, which is useful in the bottle, but has only a little practical significance because the hydrogen peroxide-ozonized is infused by venous route in the donor during the next 20 minutes and is diluted abundantly with the venous blood. Therefore, the ozone represents the medicine drug, while the pure oxygen is only required for the generation of ozone (Bocci V, Traglabi V, Zanardi I, 2011)[33, 34].

The therapeutic window has been carefully determined and oscillates between 10 and 80 µg/ml (0.21-1.68 µmol/ml) ozone per milliliter of blood. This ensures a small and accurate oxidative stress capable of causing the medical efficacy, but any toxicity[33].

The concept of a threshold is physiologically important and means that a dose of ozone below 10 µg/ml of gas per milliliter of blood, in the majority of cases, is biologically ineffective because the dose of ozone is totally neutralized by the antioxidants in plasma. In other words, the concept of a threshold helps to understand that a very low dose of ozone can be ineffective while a dose greater than the therapy may be toxic (Bocci V, Sagai M, 2011)[33].

The behavior and pharmacodynamics of H_2O_2 have been tested: the initial result of a gradient between plasma and intracellular water allows its entry in the erythrocytes, lymphocytes and platelets, but their concentration is maintained around micromoles because rapidly reduces to H_2O by free GSH, catalase and GSH-Px. Its average life is less than 60 seconds and however its intracellular concentration is essential, in order to activate some biochemical pathways (GSSG result with the consequent activation of the pentose cycle in the red blood cell and the activation of a tyrosine kinase in lymphocytes), must reach a critical threshold, however is not cytotoxic (Bocci V, Sagai M, 2011) 33. In other words, the hydrogen peroxide acts as a signaling molecule in the intracellular medium, a messenger that ozone has therapeutic doses has triggered[12].

The generation of these secondary products, which exert various biological actions in the agency, confer to ozone different therapeutic properties such as: germicide, modulator of oxidative stress and the immune system, as well as its action to improve the blood flow[12]. Ozone increases the partial pressure of oxygen in the blood, in the tissue on the aerobic metabolism, improves cellular respiration because it acts by stimulating the activity of enzymes such as glucose-6-phosphate dehydrogenase[12, 32].

It also recognizes that a moderate oxidative stress and antioxidant enzyme defense induces controlled so its oxidative properties are a mechanism that could explain the pharmacological actions of ozone in the diseases mediated by the reactive oxygen species[35], as occurs in an intoxicated person by carbon monoxide.

Also the effect of ozone on the metabolism of oxygen is of particular importance in this review. Ozone causes an increase in the rate of glycolysis of red blood cells. This leads to the stimulation of 2,3-difosfoglicerato that leads to an increase in the amount of oxygen released to the tissues. In addition, the ozone activates the Krebs cycle by improving carboxylation oxidative pyruvate, stimulating the production of ATP. The dissociation curve HbO2 moves to the right due to the effect Bohr which produce a reduction of pH small and a slight increase of 2.3 PGD. It also causes a significant reduction of NADH and helps to oxidize Cytochrome C. There is stimulation for the production of enzymes that act as sensors of free radicals and cell wall protectors: glutathione peroxidase, catalase and superoxide dismutase[36].

The main medical applications of ozone according to the specialties are: Dermatology, Internal Medicine, Nephrology/dialysis, Neurology, Odontology, Rheumatology Orthopedics, Angiology, Gynecology and immunology[12].

4.5 Chapter 5: Emergency treatment with O_3 in patient poisoned by carbon monoxide.

Carbon monoxide is produced by the incomplete combustion of carbonated materials that after his lung absorption is quickly bound to hemoglobin, taking the molecule of CO a higher affinity for hemoglobin than does oxygen [4, 5].

Nowadays the emergency treatment is the administration of oxygen to high flow, which moves the carbon monoxide from the hemoglobin, accelerating their elimination and decreasing their arrival to the cell from the bloodstream[2, 5].

Due to the properties that confer to the ozone molecule in a wide range of therapeutic indications, its use as a treatment in patient poisoned by carbon monoxide would get good results.

In order to explain this, there has been extensive literature review to prove a study that deal with this issue.

Today there is no study that has been tested the effectiveness of ozone as a treatment for a patient poisoned by carbon monoxide. Currently the studies are based on the use of oxygen with high-flow, the use of the hyperbaric oxygen therapy and the combination of certain medications reducing the appearance of sequelae.

On the other hand it has carried out an extensive literature review regarding the role of ozone in the organism as well as the main features of this molecule.

Articles consulted explain the actions of the administration of ozone in patient poisoned by carbon monoxide taking into account the limitations of this study.

According to the studies found, there is an important aspect where the ozone is capable to restore and improve the defensive duties of natural cells against oxidants and radicals, through stimulation of the enzyme systems basic protectors, such as glutathione peroxidase, catalase and superoxide dismutase Glutathione[37].

In addition another of the ozone therapy actions is to improve the metabolism of oxygen causing changes in the rheological properties of the blood, an increase in the speed of the glycolysis, an activation of the mitochondrial respiratory chain and therefore results in an increase of 2-3 PGD and therefore more ATP. Thus, the sigmoid curve moves to the right due to the effect Bohr, a fact that would be of special importance because CO produces a shift to the left of the oxygen dissociation curve with hemoglobin[12, 32, 36].

Equally the controlled application of ozone improves cellular antioxidant machinery and therefore acts as a true "cellular dump"[37], cleaning free radicals which is another aspect to be taken into account in patient poisoned by carbon monoxide that produces the formation of free radicals and a subsequent damage in our cells.

Ozone is a highly reactive molecule. In the previous chapters has been explained as the introduction of ozone in the organism reacts with the majority of organic and inorganic substances until its complete oxidation. It also highlights its influence on substances with double and triple layers among which are the proteins, amino acids and unsaturated fatty acids[12]. This reaction capacity will have influence on the molecule of CO taking into account the following reaction:

$CO + O_3 = CO_2 + O_2$

The introduction of O_3 in the organism in patient poisoned by carbon monoxide would produce a direct reaction into the molecule of CO by which will have affinity and therefore that atomic oxygen derived from the O3 molecule has a very important role to transform the molecule of CO into CO_2 and its elimination through the lungs.

Figure 1

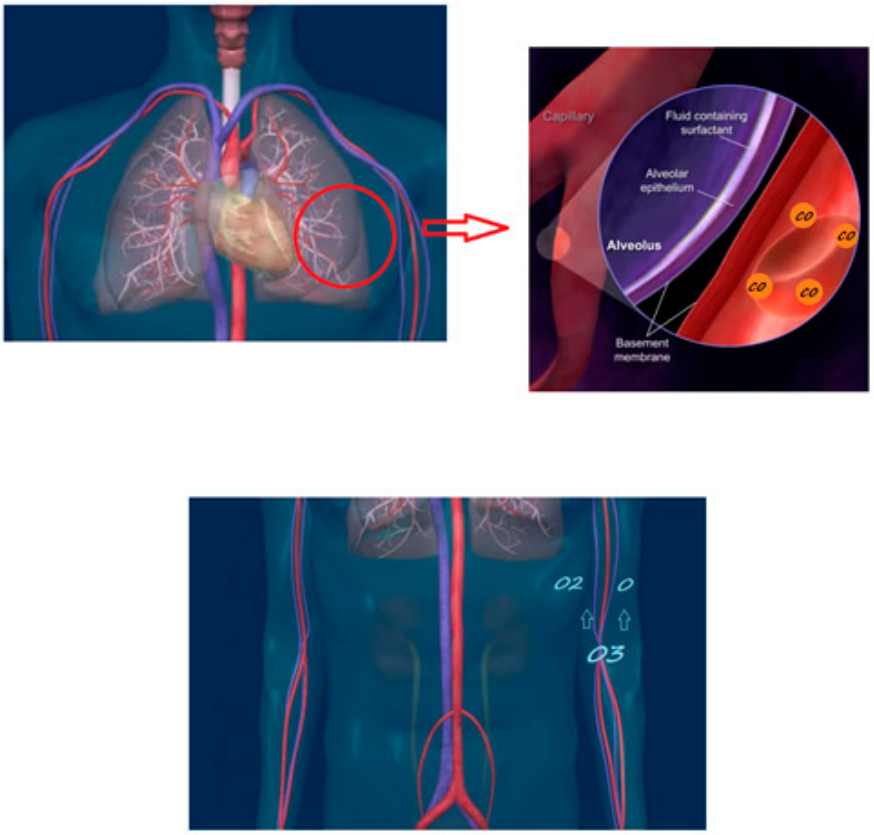
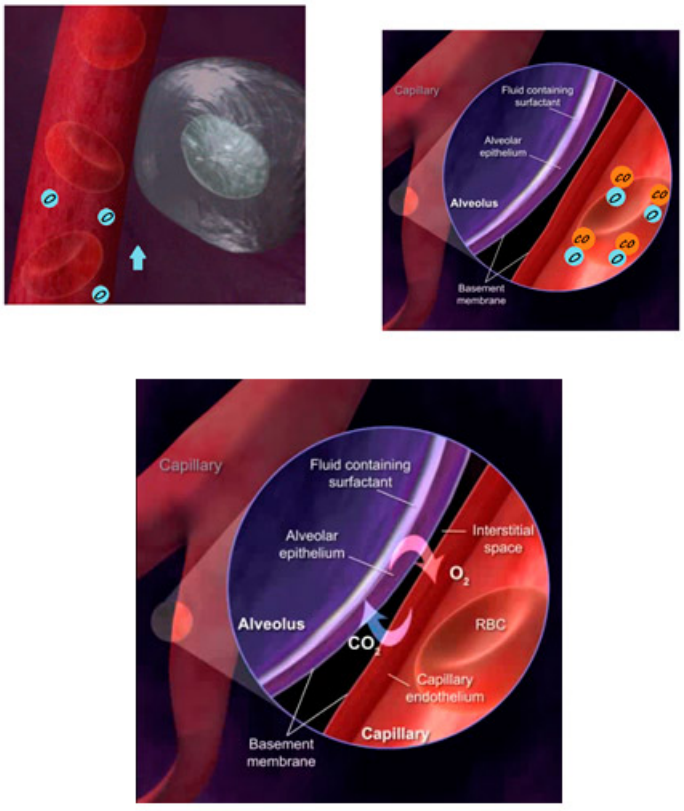


Figure 2



This explanation is only based on the properties of the ozone and its action in the body with the researches carried out over the years, it would be necessary to carry out a study in a laboratory to demonstrate whether there would be this reaction explained.

The treatment of O3 would provide a possible treatment in the carbon monoxide poisoning using the Major Auto Hemotherapy as route of administration. This route works obtaining an intravenous access and the consequent extraction of approximately 200 ml of blood in a sterile container for its subsequent introduction in the organism. Its action would be the transformation of the CO which is bonded with hemoglobin in CO2 for its elimination of the organism. In addition with a continued treatment this therapy would avoid the consequences of the late neurological syndrome that constitute a serious problem in people who have suffered this poisoning. The use of ozone therapy provides a regulation of oxidative stress and its effect on the metabolism of oxygen, getting the survival of our cells.

5. DISCUSSION

Through the literature review consulted and exposed in the present review, we can explain the importance of the treatment with ozone in patient poisoned by carbon monoxide. This provides many advantages which, as has been mentioned before, are low cost due to the production of ozone is very simple, as well as having ozone generators through which controls the therapeutic dose. Its beneficial actions in the organism makes it as a possible treatment in an poisoning by carbon monoxide with a continued use of this therapy, improving the cellular metabolism, cleaning the free radicals and ensuring the survival of the cells by preventing the future emergency alterations in our body.

According to the explanations presented throughout the study, ozone would bind to the CO molecule which is attached to the hemoglobin, to dissociate and eliminate through the lungs. As has been said at the beginning of the study, there are limitations due to the fact that the study is based on the literature review consulted and it would have to be confirmed through a laboratory.

Regardless of the limitation exposed, in the case the study is confirmed, the Ozone Therapy would become optimal treatment due to its direct action on the molecule of CO followed by a subsequent treatment with ozone continued to restore the body and cleaning free radicals generated by the poisoning, recovering those damaged cells and avoiding the so-called "late neurological syndrome".

In addition the ozone therapy would provide long-term stabilization of our organism, by stimulating the production of energy at the cellular level, maintaining an oxygenated environment and stimulate the metabolism and the antioxidant mechanism of the cell.

In comparison with the treatment used in the present, the administration of oxygen to high flow provides the improvement of a patient poisoned by carbon monoxide by moving the CO of the COHb that accelerates your elimination and diminishes its arrival in the cell from the bloodstream. However, after a few weeks of the poisoning does not prevent the occurrence of adverse effects, turning the patient back to the hospital to be attended due to dizziness, headaches, and other symptoms that presents resulting from such poisoning, leaving these radicals in our body and over time may appear diseases. This could be avoided with the use of alternative measures (as is the Ozone Therapy) being a simple technique, cheap and with beneficial results that in our study would lead to the recovery of the patient in the short and long term. In addition the currently used treatment is a high cost to treat people who have suffered a carbon monoxide poisoning.

However currently there are barriers to introduce the ozone therapy due to competition with the pharmaceutical industry which would decrease the sale of drugs due to the ozone strong power in the organism obtaining excellent results that are proving through researches carried out by different professionals who use this therapy.

The purpose with this review is to open a door of investigation to confirm the use of ozone in patient poisoned by carbon monoxide and become an effective and low cost treatment.

Today this therapy is increasingly used in different countries of the world. However, there are many professionals who are unaware of this therapy due to lack of knowledge, as well as the old concept that ozone is toxic. It has been clarified that the ozone at high doses is toxic and particularly the inhalation is very harmful. The effects at low doses have been studied and presented in scientific publications. With the continuous effort of many health professionals that use the ozone therapy, we hope that the introduction of this therapy to be accepted in the orthodox medicine in the near future.

6. CONCLUSIONS

6.1 Ozone is one of the most important discoveries during the last years in the field of medicine as a therapeutic agent, with great effectiveness, low cost and very practical.
6.2 It is one of the most controversial gases because it is useful in the stratosphere to block UV radiation but toxic in the troposphere during inhalation of air chronic.
6.3 The numerous investigations on the ozone features and the mechanisms of action have clarified its usefulness as a therapeutic agent, always taking into account the dose used.
6.4 The formation of secondary products resulting from ozone has clarified the different therapeutic properties as a germicide, modulating the oxidative stress and the immune system, as well as its action to improve blood flow.
6.5 The oxidative moderate and controlled stress induces antioxidant enzyme defense, which explains the actions of ozone in the diseases mediated by the reactive oxygen species, as in patient poisoned by carbon monoxide.
6.6 Ozone reacts with the plasma and makes part of the dose of ozone is neutralized due to the blood antioxidant capacity, while the remaining ozone will react with polyunsaturated fatty acids, as well as reaction with the molecule of CO to form CO2 and its elimination through the lungs.
6.7 The application in a patient poisoned by carbon monoxide would provide a short and long term treatment preventing the late neurological syndrome.
6.8 Nowadays the treatment in a patient poisoned by carbon monoxide consists in the administration of oxygen to high flow achieving a short term improvement but it will produce the appearance of symptoms in the next weeks.
6.9 The use of the hyperbaric oxygen therapy remains in controversy about the economic cost and the difficulty for its use.
6. 10 The ozone therapy is a fast, simple and low cost treatment and treatment for patients poisoned by carbon monoxide.

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ACRONYMS

CO: Carbon Monoxide
CO2: Carbon Dioxide
O2: Oxygen
Hb: Hemoglobin
COHb: Carboxyhemoglobin
HbO2: Oxyhemoglobin
OHB: Hyperbaric Oxygen Therapy
ROS: Reactive Oxygen Species
O3: Ozone
PUFA: Polyunsaturated fatty acid
H2O2: Peróxido de Hidrógeno
2-3 DPG: Bisphosphoglyceric acid
ATP: Adenosine triphosphate
ADP: Adenosine Diphosphate
NADH: Nicotinamide adenine dinucleotide
FADH: Flavin adenine dinucleotide
CAT: Catalase
GPX: Glutathione peroxidase
SOD: Superoxide dismutase

ANNEXES: FIGURES

-Figure 1: Imagen from book “Estructura y función del cuerpo Humano”. G.P Thibodeau ; K.T Patton. Elvesier, España, S.A; 2008. Imagen modifyied with Pain Program.

-Figure 2: Image from book “Estructura y función del cuerpo Humano”. G.P Thibodeau; K.T Patton. Elvesier, España, S.A; 2008. Imagen modifyied with Paint Program.