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New Therapeutıc Aproach in Rheumatoıd Arthrıtıs: Ozone

Gulnur Tasci Bozbas* and Omer Faruk Sendur

Department of Physical Medicine and Rehabilitation, Adnan Menderes University Medical Faculty, Aydin, Turkey

***Corresponding author:** Gulnur Tasci Bozbas, Physical Medicine and Rehabilitation Department, Adnan Menderes University Medical School, Aydin, Turkey, Tel: 0090-505-8313224.

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Abstract

Rheumatoid arthritis is an autoimmune disorder, which leads to progressive articular destruction and disability. There are numerous agents used for treatment of the disease. However, since these agents may not provide remission or lead to serious complications, search for new treatments continues today. Ozone is a complementary therapy applied successfully for long years in treatment of treatment of circulatory disorders, cancer, inflammatory diseases and various metabolic diseases and anti-aging. The effect could be seen in activation of antioxidant defense system, improvement of circulation, oxygen delivery, inhibition of cytokine release in rheumatoid arthritis. But there is need additional studies on the humans of ozone administration.

Keywords

Rheumatoid arthritis, Ozone, Cytokine, Antioxidant, Oxidative stress

Ozone is a gas, which consists of three oxygen atoms. Medical ozone therapy is a complementary treatment method in which ozone-oxygen mixture (0.05-5% O3; 95-99.95% O2) that obtained from oxygen generatore. Ozone that discovered for the first time in 1840 began to be used for therapeutic purposes since the early 1900s. It was applied successfully for long years in treatment of circulatory disorders, cancer, inflammatory diseases, various metabolic diseases and anti-aging. It has been argued that ozone affects as antimicrobial, antihypoxic, immunomodulatory, and anti-inflammatory agent [1]. The mild oxidative stress is revealed by ozone for its medical effects but no toxicity [2].

Rheumatoid arthritis (RA) is a chronic, inflammatory disease affecting approximately 1% of the population. It primarily affects the small joints in a symmetrical pattern with a potential for progressive joint destruction, and extra-articular and systemic manifestations may also be present. As the disease progresses, there are irreversible joint destruction and damage causing substantial disability. The aim of RA treatment is diminished inflammation and to decreased progression of erosion. Numerous biological and non-biological disease modifiying antirheumatic drugs (DMARDs) was used in the treatment of RA [3]. The therapy of RA remains one of the most actual problems of modern rheumatology, because in a great number of cases the best therapeutic efforts do not give expected results and are often associated with numerous complications and serious side effects [4]. Therefore, search for new treatment continues today. The interest of ozone in treating RA is increasing in recent years and several studies have been made in this issue.

How Do the Effects of Ozone in RA

The effect on cytokines

After administration, ozone is readily dissolves into H_2O_2 and aldehids such as 4-hydroksi-2E-nonenal (4-HNE) at the plasma and epithelium. H_2O_2 in plasma generates a 10% differences of gradient between plasma and intracellular area in cells [5]. Mild oxidative stress that caused by increasing of H_2O_2 in monocytes and lymphocytes activates nuclear factor-erythroid 2-related factor 2 (Nrf2) which an important cytoprotective nuclear transcription factor. Activated Nrf2 suppresses nuclear factor-kB (NF-γB) activation. NF-γB plays an important role in secretion of proinflammatory cytokine such as interleukin(IL)-8 and interferon (IF)-γ and its inhibition suppresses the releasing of these cytokines [2,6]. During each ozone therapy session, this immunmodulation appears of about 4% of the lymphocytes and monocytes present in the blood exposed to ozone ex vivo [7]. The cytokine levels in various autoimmune disease is reduced by ozone administration [3,8-11]. It has been shown that ozone decrease the cytokines such as IL-1 ve tumor necrosis factor (TNF)-α of serum, spleen homogenates and synovial fluid in RA [4,9].

The effect on antioxidants

The polymorphonuclear leukocytes (PMNs) in sinovial fluid is increase in the patients of RA. Reactive oxygen species (ROS) in which revealed in PMNs during phagocytosis disrupts the structure of hyaluronic acid, proteoglycans and collagen [12]. Thus, ROS leads to cartilage damage [2]. The antioxidants such as GSH-peroxidase, SOD and catalase play an important role the reduction of ROS. Several researchers has been suggested that enzymatic and/or nonenzymatic antioxidant systems are impaired in RA, and thus exposed to oxidant stress [13,14]. This patients are more prone to lipid peroxidation because of the reduced antioxidant defense system [15]. As a result of oxidative stress plays an important role in the pathogenesis of RA [12].

The high doses of 4-HNE which another product resulting from the metabolism of ozone is toxic to the organism. For this reason, it is rapidly metabolised by the detoxification, dilution and excretion [16]. At submicromolar or picomolar levels, 4-HNE can act as a signaling molecule, able to activate the synthesis of g-glutamate cysteine ligase, g-glutamyl transferase, g-glutamyl transpeptidase, heat shock proteins-70 (HSP-70), heme-oxygenas-1 (HO-1), and antioxidant enzymes such as superoxide dismutase (SOD), GSH-peroxidase, catalase, and glucose-6-phosphate dehydrogenase [17]. Another way to increase antioxidants after the ozone administration is through the Nrf2. Nrf2 is usually present within the cytosol as a complex with Keap-1 protein. Due to the mild oxidative stress by produced ozone, Nrf2 is released from this complex and is transported into nucleus. The transported Nrf2 forms a new complex with Maf protein, and induces the transcription of various antioxidant and phase II detoxification enzymes [2]. This step inhibits chronic inflammation in disorders such as RA, in pathogenesis of which oxidative stress plays a role [18].

Taking into account that medical ozone is a bioregulator which protects against damage by chronic oxidative stress through an oxidative pre/postconditioning mechanism [9]. The increasing of antioxidants inhibits chronic inflammation in disorders such as RA, in which oxidative stress plays a role in pathogenesis [18]. It has been shown that SOD which a potent antioxidant reduced nitrotyrosine formation and joint inflammation in RA [19]. Several experimental studies have demonstrated that controlled ozone administration could bring about a state of ozone oxidative preconditioning or adaptation to oxidative stress, preventing the damage caused by ROS [20-22]. The antioxidant capacity of plasma should not exceed more than 25% to avoid toxic effects [2].

The Effect on Clinical and Histopathological Findings

Vaillant et al. has been shown that arthritis index was decreased in the RA group of treated with 20 µg/ml ozone compared with the non-treating RA group. In this study, ozone has been applied 3 times/ week for a total 10 times and clinical effect was observed after 4 times [9]. Chen et al. has been detected to improvement in arthritis with 40 µg/ml

ozone [4]. Ozone improves not only clinical findings but also histopathological findings in RA. It has been shown that the proliferation of angioblast and new capillaries in synovial membran in RA recovered with ozone administration [9]. In addition, 5% ozone aplication for RA sinovial fibroblast cell culture have resulted in decrease an inflammation [8].

IL-17 activates nuclear factor-kappaB ligand (RANKL) which leading to NF-γB activation and thus helps to differantiation of osteoclasts in RA. Osteoclasts also play a major role to the development of erosion in RA [23]. Nrf2 which increasing with ozone administration can prevent erosions in RA by supressing NF- γB activity. In addition, osone can be benefical in the prevention of RA dependent systemic osteoporosis [2,24].

The studies on ozone treatment of RA is very limited and we need additional studies on the humans of ozone administration.

Therapeutic Dose in Rheumatoid Arthritis

The response of organism to ozone is dose-dependent. In order to acquire a stimulating and suppressing effect, the chosen dose varies according to the oxidative load and antioxidant capacity of tissue to be applied. The “therapeutic window” for O3 was stated as 10-80 µg/ml [2]. In applications with doses under the necessary dose, a response cannot be obtained and in unnecessarily high doses, since the antioxidant capacity is exceeded, carbohydrates, enzymes, DNA, and RNA might be affected by the reactions. An ozone concentration below 10 µg/ml is in most cases totally quenched by the hydrosoluble antioxidants and therefore no biological effects can be elicited [17]. Chen et al. were determined that exacerbation of arthritis was found to emerge with 50 µg/ml dose of O3 in treatment of RA, and the most effective dose was reported to be 40 µg/ml [4]. In other study, after intraarticular osone administration with a dose of 20 µg/ml, improvement in arthritis index was detected [9]. Ozone is administrated via major autohemotherapy, intrarectal and intraarticular in RA [4,9].

There is neither damage to erythrocytes nor to other cells: hemolysis is negligible (from 0.4 up to 1.2%), there is no leakage of K+ and methemoglobin remains normal [25]. As well as no toxic effects have been observed [4,9,19-21,26].

In conclusion; ozone is an effective and reliable complementary therapy that can used in treatment of RA. But it is quite assertive to say that the use of ozone alone cures the RA. Nevertheless it can reduce to need for DMARD's or accelerate to occurence of remission. Ozone should be applied as support of medical treatment, as soon as diagnosis of RA.

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