Protective effect of rectal ozone therapy against oxidative stress in immunoglobulin A deficiency.

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Summary
The excess production of free radicals produces an imbalance between the prooxidants and antioxidants in favor of the former; which causes loss of redox control signaling and damage to biomolecules such as proteins, lipids and deoxyribonucleic acid. When homeostasis is altered in the redox metabolism of cells that participate in the immune response, they usually evolve into a situation of oxidative stress that facilitates cell dysfunction and death. The objective of our work was to study the effect of ozone on the regulation of redox status, necessary to maintain normal immune function in patients with immunoglobulin A deficiency. Patients and methods: The Research Ethics Committee conducted and approved a clinical trial and informed consent was taken for inclusion. Sixty patients were randomly assigned to two groups: one receiving ozone rectal insufflation (study group-SG) and the second using Hebertrans® (control-GC group), subcutaneously. Pro-oxidant parameters (malondialdehyde-MDA and advanced oxidation protein products-AOPP) and antioxidant parameters (superoxide dismutase1-SOD1, catalase-CAT, glutathione peroxidase-GPx and total antioxidant capacity of serum) were measured. They were measured at the beginning and one month after treatment. Results: In the SG the MDA and the APOP of patients ≤15 years, decreased significantly (p = 0.000) with respect to the control group. SOD1 in the SG increased in patients ≤15 years (p = 0.006) and from 16 to 30 years of age (p = 0.040) with respect to GC. CAT in patients ≤15 years of the SG increased significantly (p=0.001) with respect to initial values. The final result of the total antioxidant capacity in the SG was significantly (p=0.000) higher in patients ≤15 years, similar results were obtained in GPx (p=0.013).

Conclusions:
With ozone therapy, beneficial effects of the reduction in oxidation balance were achieved. Medical ozone therapy may be an additional treatment option, for immunoglobulin A deficient patients with oxidative stress.

Key words:
Ozone therapy, prooxidants, antioxidants, oxidative stress, redox, IgA deficiency.
INTRODUCTION

During the immune response against invasion by pathogens, the release of oxidants that cause cytotoxic effects and death of microorganisms occurs. Phagocytic cells activate the nicotinamide adenine dinucleotide phosphate oxidase (NADPH-oxidase), enzyme in the plasma membrane, to produce the superoxide anion (O$_2^\cdot$•). The activity of phagocytic NADPH-oxidase constitutes one of the most important endogenous sources of reactive oxygen species (ROS) in the body, catalyzes the univalent reduction of molecular oxygen with the consequent production of O$_2$••. In quiescent phagocytes (at rest), NADPH-oxidase is not active, but acquires catalytic activity when cells are stimulated with appropriate agents. B lymphocytes and other non-phagocytic cells also express this enzyme. On the other hand, neutrophil polymorphonuclear cells are phagocytic cells that activate the myeloperoxidase enzyme to form hypochlorite (OCl-) and hypochlorous acid (HOCl) from hydrogen peroxide (H$_2$O$_2$) and chlorine (Cl-), which have potent cytotoxic action. The effect of the activation of these cells determines an oxidative stress (OS) condition in the microorganism with cytotoxic effect (1).

The endogenous antioxidant system protects against free radical (FR) damage. Primary antioxidants prevent overproduction of FR or convert them into less harmful molecules, before they react with vital structures. In this group, SOD, GPx, CAT, among other enzymes stand out. Secondary antioxidants capture FR and prevent chain reactions, examples of them are: vitamins C and E, β-carotenes, uric acid and bilirubin.

The redox imbalance during the immune response produces inflammatory OS, which has an impact on the clinical manifestations and the therapeutic response of the patients (2). Inflammatory oxidative damage causes an increase in the production of proinflammatory cytokines and continuous generation of oxidizing compounds, such as O$_2$••, H$_2$O$_2$, hydroxyl radical and nitric oxide (2,3). Redox imbalance and chronic OS in primary immunodeficiency diseases (PIDD) such as Bloom’s syndrome and ataxia telangiectasia are reported in the scientific literature (4). Another study reports OS participation in human immunodeficiency virus infection both due to overproduction of ROS, as well as antioxidant deficiencies (5). Redox imbalance exerts a detrimental effect on cell homeostasis and could be responsible for clinical manifestations in PIDD that are not related to the genetic defect that characterizes it.

Immunoglobulin A deficiency (IgAD) is a PIDD that belongs to the group of disorders with predominant deficit in antibody production. It is the most common PIDD and the worldwide incidence varies depending on ethnic origin (6). The definitive diagnosis of IgAD is established according to the criteria defined by the European Society Immunodeficiency (ESID), which classifies the IgAD according to its clinical presentation in two categories: with complete and partial deficit (7). IgAD has no specific treatment, nor is there replacement therapy. Infections are treated with antimicrobials according to the sensitivity of the causal germ and some patients need prolonged prophylactic treatment to avoid complications and organic damage (8).

The frequent or prophylactic use of antimicrobials in patients with IgAD, favors the development of bacterial resistance and the occurrence of adverse reactions.
(destruction of the microbiota and superinfections). The application of blood products containing IgA is not recommended due to the risk of anaphylactic reaction (9). Hebertrans®, with beneficial clinical effects in this immunodeficiency (10), constitutes a nonspecific treatment that is not, in all cases, beneficial from the point of clinical view and is not available in a stable manner in pharmacies, which makes it difficult to acquire when needed. Limitations in treatment guide the search for other options that are not invasive and are effective in increasing the immune response, particularly against infections that occur in these patients. There is scientific evidence of the immunomodulatory and antioxidant effect of ozone therapy (O3T) and its safety in preclinical and clinical investigations, which support its use in different medical protocols (11-13). In addition, it constitutes an economically feasible therapeutic procedure and social (14).

The lack of controlled clinical trials and approved by regulatory bodies, with the aim of evaluating the efficacy and safety of rectal O3T in different diseases, including those of the immune system, make this study necessary in patients with IgAD.

Taking into account that O3T is able to stabilize the redox balance in various diseases, we set out to determine the effect of O3T on the redox balance in patients with IgAD.

METHODS AND PATIENTS

This study is a controlled clinical trial (registration code: RPCE 00000236), randomized (phase II) and monocentric, conducted in “Captain Roberto Rodríguez Fernández” General Hospital, located in Ciego de Ávila province, Cuba, with the joint participation of other centers such as the Institute of Hematology and Immunology (IHI) and the National Center of Medical Genetics (NCMG), both located in Havana, Cuba. Sixty patients ≥ 5 years of both sexes were selected, with a diagnosis of IgAD that met the inclusion criteria: presence of absolute and partial IgAD, according to what is established by the ESID, who issued their written consent to participate in the investigation, after having received information on the characteristics of the study. Patients who received blood transfusions, three months prior or during the study, immunomodulatory drug treatment, six months prior to the start of the study, were excluded; also those who received medications that decrease IgA transiently, three months prior or during the study and those who presented any medical contraindication to receive Hebertrans® or O3T.

The included patients were randomly assigned to two treatment groups: a study group (SG) that received rectal treatment with O3T, and a control group (CG) that received Hebertrans® subcutaneously.

The administered medical ozone (O3) consists of the mixture of oxygen (95%) and O3 (5%), obtained from the OZOMED plus generator (CNIC, Havana, Cuba). Two cycles of O3T treatment were applied by rectal insufflation, of 20 sessions each (40 sessions in total), with an interval of three months between cycles, in daily applications (Monday to Friday) and weekly staggered doses, with regards to the dosage calculated according to age (15,16).
The CG was administered Hebertrans® (Center for Genetic Engineering and Biotechnology, Havana, Cuba) according to the following scheme: 1 Unit per m² of body surface, diluted in 1 mL of water for injection, subcutaneously and administered in the deltoid region, with a weekly frequency in children and twice a week in adults, for 16 weeks (17).

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Dose (mg)</th>
<th>Concentration (mg/L)</th>
<th>Volume (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 - 10</td>
<td>1,2 - 3</td>
<td>25 - 30</td>
<td>50 - 100</td>
</tr>
<tr>
<td>11 - 15</td>
<td>2,2 - 4,2</td>
<td>30 - 35</td>
<td>75 - 120</td>
</tr>
<tr>
<td>16 - 50</td>
<td>3,5 - 8</td>
<td>35 - 40</td>
<td>100 - 200</td>
</tr>
</tbody>
</table>

To evaluate the parameters of OS, 5 ml of blood was taken and placed in a tube with ethylenediaminetetraacetic acid, plasma and erythrocyte lysate were obtained, the samples were stored at -20°C until the time of processing (no more than ten days). The plasma concentration of MDA was determined from the method described in the BIOXYTECH® LPO-586TM assay (OXIS Research, Portland, USA). The technique was based on the reaction of two molecules of the chromogenic reagent, N-methyl-2-phenyl indole, with a molecule of MDA at 45°C, which leads to the formation of a stable chromophore with a maximum absorbance at 586 nm on the VS-850 spectrophotometer. The results were expressed in μmol/L (18). The AOPP plasma determination was performed using the spectrophotometric technique described by Witko Sarsat et al. This indicator shows the degree of oxidation of plasma proteins, especially albumin, mediated by the action of chlorinated oxidants, such as hypochlorous acid, released by activated neutrophils. The technique is based on the fact that AOPP react in the same way as chloramine T (standard) with potassium iodide in an acid medium. This reaction yields a colored compound that absorbs at 340 nm in the VS-850 spectrophotometer. The results were expressed in μmol / L (19).

The intraeritrocyte activity of the SOD1 enzyme (Cu/Zn isoform) was determined by the spectrophotometric technique described by Marklund et al. It is an indirect kinetic method, which is based on the ability of this enzyme to inhibit the auto-oxidation reaction of pyrogallol. Its oxidation results in purpurogaline, a yellow-brown compound, by which the magnitude of the reaction is estimated. It is a kinetic test that runs for one minute under optimal conditions of pH and temperature (pH = 8.20; T = 25 °C). The reading is carried out at 420 nm optical density units, in the Spectronic Genesys 8UV-VIS spectrophotometer. In order to calculate the activity, it is taken into account that a unit of enzymatic activity is capable of inhibiting 50 % of the autooxidation of pyrogallol. The units are expressed in % inhibition / minute / ml of enzyme (U mL) (20). The determination of the enzymatic activity of CAT was performed using the direct kinetic method referred to by Aebi H. et al (21). The technique uses H2O2 as a substrate and measures the decomposition of this substrate, by the action of the enzyme present in the sample, reaction that is followed by the variation in the optical density, in one minute, at a wavelength of 240 nm. The reading was performed on the Ultraviolet/visible Spectrophotometer (PHARMA SPEC UV 1700).
Enzyme activity units are expressed in mmoles of transformed H2O2/minute/ml of enzyme (U/mL). The determination of the intraeritrocyte enzymatic activity of GPx was performed using the technique referred to by Paglia DE and Valentine WN. The reaction is initiated by the addition of the H2O2 substrate. The reading was performed on the PD-303S Spectrophotometer at 340 nm in the kinetic mode of the equipment. Enzyme activity units are expressed in mU/mL (22).

Total antioxidant capacity measures the contribution of plasma components to reduce oxidized substances. It was performed using the Ferric Reducing Ability of Plasma (FRAP) test, which uses iron as a redox system and determines the ability of the plasma to reduce ferric ions to ferrous. The reduction of ferrous to ferrous ion at a low pH results in the formation of the Fell-Tripyridyltriazine complex, a blue chromogen that was measured, after four minutes of reaction in the PR-521 plate reader with the 530 nm filter. The results were expressed in mM equivalents of Fell/L (23).

**STATISTIC ANALYSIS**

The results obtained were processed using the SPSS version 21.0 program and expressed as absolute values and percentages. The independence and homogeneity test (as the case may be) with Pearson’s chi-square distribution was used to evaluate the relationship between nominal variables and their Yates continuity correction variant for 2x2 tables.

For categorical variables, the Mann-Whitney U test was used to evaluate quantitative variables that did not follow normal or ordinal distribution in 2 independent samples. For related samples, the Wilcoxon signs ranks test was used for quantitative variables that did not follow normal or ordinal distribution in 2 related samples. The Friedman test was used to evaluate quantitative or ordinal variables in k related samples.

**RESULTS**

The number of patients distributed for age according to the ranges of normal reference values, determined a greater number of patients ≤15 years (27 in the SG and 22 in the CG) with respect to patients from 16 to 30 years (two cases in the SG and seven in the CG) and ≥31 years (one patient in the SG and another in the CG) whose results were analyzed by non-parametric tests. The inclusion of a greater number of patients> 15 years in each group would be feasible to demonstrate with greater precision, the effect of the treatments.

The comparison between the treatment groups according to the values of prooxidant parameters, showed that there were no significant differences between them for the MDA and for the AOPP (Table 1) before starting the assigned treatment. According to the results of the measured prooxidants the groups were homogeneous.

When comparing the values of prooxidants (MDA and AOPP) with the normal reference values according to age, it was detected that the MDA was high in the SG in 21 patients (70%) and in the CG in 25 (83.3%) and AOPP were high in the SG in 17 patients (56.7%) and in the CG in 15 (50%).

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The comparison between both groups (SG and CG) in relation to the pro-oxidant parameters one month after finishing treatment showed that MDA and AOPP of patients ≤15 years, decreased significantly (p = 0.000) in the SG with respect to the CG (Table 1).

In both groups the final results of MDA and AOPP of patients ≤15 years, were significant with respect to the initial values (p= 0.000). In patients aged 16 to 30 years in both group, the decrease in parameters was not significant with respect to the initial results.

Table 1.
Initial and final analysis of the pro-oxidant parameters according to the treatment group.

<table>
<thead>
<tr>
<th>Pro-oxidantes</th>
<th>Treatment group</th>
<th>Study group</th>
<th>Control group</th>
<th>P1</th>
<th>P2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean ± SD</td>
<td>Mean ± SD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDA</td>
<td>≤15 years</td>
<td>Initial</td>
<td>1,1 ±0,6</td>
<td>1,3 ±0,6</td>
<td>0,113</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>0,7 ±0,1</td>
<td>1,1 ±0,4</td>
<td>0,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0,000</td>
<td>0,000</td>
<td></td>
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<tr>
<td></td>
<td>16-30 years</td>
<td>Initial</td>
<td>1,0 ±0,0</td>
<td>1,2 ±0,5</td>
<td>0,770</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>0,7 ±0,2</td>
<td>1,2 ±0,4</td>
<td>0,143</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0,180</td>
<td>0,249</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥31 years</td>
<td>Initial</td>
<td>2,3</td>
<td>2,3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>0,9</td>
<td>2,2</td>
<td>-</td>
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<td></td>
<td></td>
<td></td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>AOPP</td>
<td>≤15 years</td>
<td>Initial</td>
<td>49,3 ±10,5</td>
<td>52,1 ±5,6</td>
<td>0,252</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>40,6 ±10,6</td>
<td>51,2 ±5,3</td>
<td>0,000</td>
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<td></td>
<td></td>
<td></td>
<td>0,000</td>
<td>0,000</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16-30 years</td>
<td>Initial</td>
<td>55,0 ±5,8</td>
<td>44,2 ±17,8</td>
<td>0,380</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>50,2 ±1,6</td>
<td>49,4 ±7,7</td>
<td>0,770</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0,655</td>
<td>0,310</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥31 years</td>
<td>Initial</td>
<td>58,9</td>
<td>55,9</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Final</td>
<td>52,5</td>
<td>55,9</td>
<td>-</td>
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</tbody>
</table>

1 U de Mann-Whitney  2 Wilcoxon signed ranks test

Legend: Study Group: (≤15 years, n = 27), (16 to 30 years, n = 2), (≥30 years, n = 1). Control Group: (≤15 years, n = 22), (16 to 30 years, n = 7), (≥31 years, n = 1)
When comparing the antioxidant parameters in the SG and CG a month after receiving the treatments, it was evidenced that the SOD1 (figure 1) in the SG was significantly higher in patients ≤15 years (p= 0.006) and from 16 to 30 years of age (p=0.040), compared to the CG. Significant results were obtained when comparing the values at the beginning and at the end in the SG, in patients with age ≤15 years (p=0.000 ) and between 16 and 30 years (p= 0.0189).

The CAT analysis is shown in figure 2. When comparing the results at the end between the SG and the CG, it showed that there were significant differences (p= 0.040) in the results of patients aged 16 to 30 years. On the other hand, in patients ≤15 years of the SG, the results at the end were significantly (p=0.001) higher with respect to the values at the beginning. CAT when catalyzing the decomposition of H2O2 into H2O and O2, is of great importance in maintaining redox equilibrium.
When comparing the FRAP results between the groups (figure 3), higher values were found at the end in the SG with respect to the CG, although this increase was found to be non-significant (p = 0.271) in patients ≤15 years and in patients between 16 and 30 years (p = 0.883). The initial and final analysis within each group showed that in the CG the FRAP values at the end were not higher than at the beginning in any age range. On the other hand, in patients ≤15 years of SG, the outcome at the end was significantly (p=0.000) higher than the onset. This evidences the positive effect of O3T on the total antioxidant capacity of plasma to oxidative damage.

![Graph showing FRAP values at the beginning and at the end according to age and treatment group.](image)

**Figure 3.**
Ferric Reducing Ability of Plasma values at the beginning and at the end according to age and treatment group.

When comparing the GPx results between the groups (Figure 4), higher values were found at the end in the SG with respect to the CG, this increase was not significant (patients ≤15 years, p=0.103; 16-30 years, (p = 0.242). When comparing the results at the beginning and end in the SG, significant differences (p=0.013) were evidenced in patients ≤15 years.
DISCUSSION

The high levels of MDA and AOPP in the majority of patients in both treatment groups show that there is a redox imbalance with a predominance of the prooxidant state. This evidence is consistent with the results of other authors in immunological diseases of different etiology, such as: PIDD, AIDS and systemic lupus erythematosus (SLE). (4, 5, 24)

The redox imbalance in the IgA deficient patients of the study led to an inflammatory OS, as a result of hyperactivity of the enzyme NADPH-oxidase and exaggerated production and accumulation of oxidants such as O2•− that cause tissue damage, such as: lipid peroxidation, reaction with other FR, such as nitric oxide (NO−) and the formation of other more harmful radicals such as peroxynitrite (ONOO−). Lipid peroxidation by FR causes nonspecific oxidation of polyunsaturated fatty acids, breakdown of the lipid structure and as a consequence, loss of membrane integrity. MDA is a marker of this process, of clinical relevance since it constitutes a toxic aldehyde that propagates the peroxidation chain (25). The elevation of AOPP in patients is a product of the effect of FR on proteins (26). On the other hand, the neutrophil uses myeloperoxidase to clarify H2O2 during the immune response, and as a reaction product generates hypochlorous acid. However, in situations of hypercatabolism such as recurrent and chronic infectious diseases, 40% of H2O2 is converted into hypochlorite and 60% is hydroxyl anion. The uncontrolled increase in H2O2 in the presence of metals such as iron (Fenton reaction) also generates hydroxyl anion. These radicals act on biological molecules such as lipids, proteins and nucleic acids, with MDA being a product of lipid oxidation and AOPP being a product of protein oxidation (3, 26, 27).

Enzyme antioxidant defense systems constitute the first line of cellular defense against oxidative damage, since they act on ROS degrading them to simpler molecules. SOD decreases O2•− and CAT and GPx
eliminate H2O2 and organic peroxides, so they must be in balance to maintain the intracellular redox balance (28).

Immune system cells are strongly influenced by redox balance, since changes in redox metabolism occur to carry out their functions. Cells that have cytotoxic and phagocytic function are sensitive to changes in this balance, since due to their microbiocidal activity they generate FR and suffer deterioration with OS (26,29). The redox imbalance identified in the patients of the present study could be due to infectious diseases, recurrent and chronic bacterial diseases, diagnosed in symptomatic IgA deficient patients, pro-inflammatory status, and allergic and autoimmune diseases that coexist with this PIDD.

The mechanisms that are involved in inflammatory OS are the recruitment of inflammatory cells, interference with antioxidant defenses, increased intracellular calcium and increased activation of the enzyme NADPH-oxidase that generates O2•-, which in the presence of iron ions passes to be hydroxyl and this radical is of high toxicity. The inflammatory OS is associated with immune dysfunction, which affects the clinical picture and the therapeutic response in patients with immune diseases that manifest it (4,5,24,30), so it is important to correct it.

SOD regulates the accumulation of O2•-, the most abundant radical in cells, which forms in the electron transport chain and during phagocytosis as a bactericide. Its accumulation is associated with lipid peroxidation and is a precursor to other more harmful radicals (2,28). The significant increase in SOD after O3T is important as it catalyzes the dismutation of O2•- into oxygen and H2O2. The increase in SOD1 due to the effect of O3T indicates that O2•- decreased and the formation of ONOO• was avoided, a radical formed by the reaction of O2•- with ON•. The increase in GPx is important in the redox balance, since this enzyme catalyzes the reduction of H2O2 to water and lipoperoxides to alcohols (26,28).

The antioxidant effects of O3T rectally were reported by Calunga et al. (31) and Borrego et al. (32) in experimental models. Other authors evidenced the antioxidant effect when applying medicinal O3 by rectal insufflation in clinical trials (33,34). The antioxidant effect of O3T is based on the ability of medicinal O3 to stimulate endogenous antioxidants, without causing harmful effects (31,35). This mechanism involves the activation of kinases and transcription factors that induce the expression of genes encoding antioxidant enzymes. It was shown that O3 stimulates the transcriptional factor Nrf2, which translocates from the cytosol to the nucleus, binds to the Maf protein and induces the transcription of several enzymes, including antioxidants, by binding to antioxidant response elements in deoxyribonucleic acid (36).

Several transcription factors were identified by Bocci V. in peripheral blood cells activated by O3, such as: Nrf2, NFAT, AP-1 and NF-kB (37). The transcription factors NFAT, AP-1 and NF-kB, participate in intracellular signaling pathways for the activation of T and B lymphocytes (27). Re L. et al. demonstrated the stimulation of Nrf2, after administering O3T to healthy volunteer individuals (38). Other authors assert that Nrf2 is the crucial mediator of the response to O3 in vivo and in vitro, considering it fundamental in the modulation of mitochondrial function under conditions of stress to maintain cell homeostasis. They observed in vitro, a higher transcription rate in cells treated with O3 and an increase in the expression of genes involved in the stress response (39).
The relevance of this result is that, by increasing antioxidant enzymes, they prevent FR from damaging vital structures, stop the production of new oxidizing molecules and favor the cells moving into a “reduced environment”. In this way, the integrity of the membranes and the specific functions that, in the case of immune system cells, is the defense against pathogenic microorganisms are preserved (27,28).

The induction of antioxidant defense systems is one of the most important mechanisms to limit the formation of oxidative damage induced by ROS and to regulate its biological activity in several diseases (40). Other authors report similar results in clinical investigations with O3T (41, 42, 43). The scientific evidence of the effects of medicinal O3 at the cellular level (44,45), allows us to assert that O3T favored the response to the endogenous antioxidant response.

CONCLUSIONS

An imbalance in redox metabolism was evident with a predominance of the prooxidant state in IgA deficient patients, which may have an impact on the progression and severity of the disease. O3T stabilized the cellular redox balance by stimulating antioxidant defenses and decreasing pro-oxidant parameters. The treatment scheme, adjusted to age, was beneficial for this primary immunodeficiency.

BIBLIOGRAPHIC REFERENCES


