

OZONE THERAPY IN UROLOGY

Review Article

ÜROLOJİDE OZON TEDAVİSİ

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ABSTRACT

For the first time, ozone was used during World War I to treat soldiers having gangreen. It is now accepted as a reliable medical therapeutic method. Ozone therapy is application of a gas mixture comprising ozone/oxygen into body cavities and circulation. Ozone is used in multiple applications in medicine with its low adverse effect. Its usage in urology especially in ischemic and chronic diseases is getting increase by the time passed.

Key words: Urology, ozone therapy.

ÖZET

İlk defa 1. Dünya Savaşı sırasında askerlerin gangren tedavisinde kullanılmış olan ozon tedavisi artık güvenli bir medikal tedavi yöntemi

olarak kabul edilmektedir. Ozon tedavisi ozon/oksijen karışımının vücut boşluklarına ve dolaşım sistemine uygulanmasıdır. Ozon düşük yan etkisiyle tıpın pek çok alanında uygulanmaktadır. Zaman geçtikçe ozonun üroloji alanında özellikle iskemi temelli ve kronik hastalıklarda kullanımı da artmaktadır.

Anahtar kelimeler: Üroloji, ozon tedavisi

INTRODUCTION

Ozone

Oxidant generation is part of the normal metabolism of many cell types and is critical for homeostasis. An antioxidant system in our bodies protects against oxidative stress—a state of imbalance between oxidant production and antioxidant defenses. Oxidative stresses have been implicated in the pathogenesis of many acute and chronic diseases. However, natural defense mechanism of the body is not sufficient to relief the injury and disease process. Thus, we need a treatment which is able to stabilize oxygen metabolism and modulate oxidative stress to restore the homeostasis.

DISCUSSION AND REVIEW

Ozone as Therapy

Ozone could be a good therapeutic agent. Medical ozone therapy is a gas mixture comprising ozone /oxygen. Ozone has been investigated as a therapeutic agent for the treatment of different diseases mediated by free radical oxygen species (ROS) (1-3). Ozone was able to stimulate the endogenous antioxidant defense systems and prepare the host to face ischemia-reperfusion injury (2-4). This phenomenon was called "ozone oxidative preconditioning". It was declared that ozone was a simple and harmless method that provides a tool to protect organs from ischemia-reperfusion injury. Ozone has therapeutic properties of antiplatelet

activity, enhancement of cell energy, increase of the antioxidant defense system (4).

Clinical studies have so far shown therapeutic effects of ozone therapy in diseases including orthopedic diseases, diabetes mellitus and its complications, eye diseases, peritonitis, infected wounds, chronic skin ulcers, initial gangrene, burns and ischemic conditions.

In the field of urology, main pathophysiologic mechanism of many diseased processes is ischemia-reperfusion pathology, such as, renal ischemia, testicular torsion, erectile dysfunction pathologies, chronic cystitis and chronic pain syndromes.

Ekici et al. designed an ischemia-reperfusion injury experimental model to compare the therapeutic effect of ozone with melatonin, which is known as a potent and therapeutic antioxidant agent (5). In an experimental model of unilateral testicular torsion performed on twenty-four healthy 3-month-old male Wistar rats, the biochemical parameters characterizing the oxidative stress were evaluated under ozone treatment and compared with those obtained with melatonin. The authors reported that ozone therapy had benefits in the treatment of testicular torsion with respect to the biochemical and histopathologic parameters. Its effectiveness was comparable with melatonin.

The pathophysiologic mechanism of ischemia-reperfusion injury is not totally clarified. During ischemia, the limited oxygen availability leads to lower adenosine triphosphate (ATP) production, with degradation of ATP to adenosine and then to hypoxanthine. Loss of calcium-pumping activity leads to increased intracellular Ca^{+2} concentration, which in turn led to the activation of the calcium-dependent metabolic activities with membrane damage and proteolytic conversion of xanthine dehydrogenase to xanthine oxidase (6). Although reperfusion is essential for the survival of ischemic

tissue, reperfusion itself causes additional further cellular injury in tissue. Reperfusion injury develops in 2 phases. The first phase occurs immediately following reperfusion, lasts for a few hours, and is reversible (6,7). This phase is featured by mitochondrial dysfunction, failure of oxidative phosphorylation, and toxic burst of ROS generation. Superoxide anions are produced by xanthine oxidase in parenchymal cells and polymorphonuclear leucocytes (6). Under physiologic conditions, ROS produced during cell metabolism are rapidly scavenged by endogenous antioxidant systems. Nevertheless, oxidative stress is featured by an imbalance between excessive ROS and the antioxidant systems (6). Excessively produced ROS react with lipids in the cellular and mitochondrial membranes, proteins, and DNA, causing to cellular dysfunction and disruption of membrane integrity (6,8). The second phase lasts for hours or days and is characterized by irreparable tissue damage and inflammation (6). Ozone therapy performs as an efficient oxidative stress regulator and can trigger several useful biochemical mechanisms and reactivate the antioxidant system on the basis of the phenomenon of hormesis and together produce an adaptation to oxidative stress (2).

The basic mechanisms of ozone oxidative preconditioning have not been yet fully clarified. When therapeutic ozone joins into the blood circulation, ozone dissolves in the plasma and reacts immediately with several substrates, mainly polyunsaturated fatty acids and -SH groups, such as GSH, present in several molecules. The reaction produces H_2O_2 and lipid hydroperoxides at low concentrations, which may behave as cellular signals and activate the cellular cytoprotective signaling pathways, augmenting the antioxidant capacity and some enzymes related to the glutathione synthesis against forthcoming oxidative stress, reducing the excessive production of ROS (9,10). Ozone displays potent anti-inflammatory and anti-apoptotic properties and can reduce the ATP

depletion and blocks the formation of xanthine oxidase (11). As a result, preserved adenosine regulates smooth muscle tone to causes vasodilation and other mechanisms to activate antioxidant enzymes (12). Moreover, ozone adjusts calcium levels, maintaining its homeostasis by protecting Ca^{+2} adenosine triphosphatase activities (13). In addition, ozone treated erythrocytes show an improved glycolysis with an increase of ATP and 2,3-DPG levels, which are able to shift the dissociation curve of HbO₂ to the right, causing to an improved delivery of oxygen in peripheral tissues (10). As a result, ozone regulates the balance in favor of vasodilators against vasoconstrictors, which in turn causes to regression of "no-reflow" phenomenon, characterized by failure of reperfusion of ischemic tissue.

The concentration of protein sulfhydryl and GSH is often used as an index of oxidative stress (14). It was reported that ozone therapy increased GSH levels and decreased plasma sulfhydryl (10,14). It has been shown that exposure to ozone leads to oxidation of plasma sulfhydryls (14). This may cause a decrease in RSH levels following ozone therapy.

Nitric oxide (NO) has a protective effect on vasodilatation, anti-apoptotic action, inhibition of platelet plug formation, and reduction of the inflammatory response (15). NO performs locally to regulate the distribution of oxygen, nutrients, and hormones by the testicular vessels. The features of NO depend on which isoform of NO synthase (NOS) is activated. Endothelial nitric oxide (eNOS) and neuronal nitric oxide (nNOS) are inherently expressed and contribute to the physiologic regulation of vascular tone and neurotransmission (16). On the other hand, NO rapidly reacts with superoxide, leading to produce very reactive peroxynitrite, which is able to induce tissue injury (6). In ischemia-reperfusion injury, all three NOS isoforms are involved in the pathology. Especially, NO is synthesized by eNOS

and inducible NOS (iNOS). Ischemia-reperfusion injury may reduce the transcription of eNOS and activate iNOS during reperfusion (6,16). After reperfusion, the infiltration of PMNL in the interstitial tissue further expressed iNOS, leading to cell death with the predominance of necrosis over apoptosis (16). Nevertheless, the role of iNOS in ischemia-reperfusion injury is still controversial. Some recent experiments confirmed that eNOS-generated NO played a pivotal protective role in ischemia-reperfusion injury and iNOS generated NO inhibited ischemia-reperfusion injury. iNOS deficiency produces unanticipated genetic alterations that render mice more sensitive to ischemia-reperfusion injury (4). Ozone activates the genes associated to both eNOS and iNOS, which promotes NO formation in the required concentrations for protecting against ischemia-reperfusion injury.

CONCLUSION

In summary, although ozone is widely used as a medical therapy, cellular and molecular mechanisms on which ozone exerts its therapeutic effects are a wide field of research.

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