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The chemotherapy-induced peripheral neuropathy treatment with novel systemic ozone therapy method: A case report

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Abstract

Cancer is one of the leading causes of death in the world today. Chemotherapy is promising to overcome it, but chemotherapy accompanies with side effects. Among these side effects can be pointed to Chemotherapy-Induced Peripheral Neuropathy (CIPN). CIPN decreases the quality of life of sufferers and increases the cost of care. This report mentions a new method based on systemic ozone therapy for the treatment of pain caused by CIPN. A patient with severe pain (NRS score of 10) caused by CIPN was treated with the innovative method of systemic ozone therapy. This method is based on the use of ozone gas mixture infusion with a dose of 50 µg/cc with half-saline, and the volume of ozone in the mixture increases upto 100 cc during subsequent sessions. During ten treatment sessions, the pain score reached about three and showed a significant decrease.

Keywords: Peripheral neuropathy; Ozone therapy; CIPN; Pain.

Introduction

Cancer is now the leading cause of death around the world. The drugs used in cancer chemotherapy act like a double-edged sword, in addition to useful effects in cancer treatment, they also cause several side effects [1]. Chemotherapy agents can damage the structures of the nervous system and cause a variety of neuropathies, including large and small nerve fibers, sensory or motor, cranial or autonomic, and demyelinated and axonal [2]. Peripheral neuropathy can manifest in many different patterns. Damage to peripheral nerves can lead to motor and sensory defects. Sensory manifestations can be a mixture of hyperesthesia and hypoesthesia [3]. One of the most common neuropathies caused by antineoplastic agents is called Chemotherapy-Induced Peripheral Neuropathy (CIPN). CIPN is a common side effect of anticancer agents that often presents with sensory symptoms rather than motor ones [4].

One of the most common neuropathies caused by antineoplastic agents is called chemotherapy-induced peripheral neuropathy [4]. The main mechanisms proposed for the development of CIPN include mitochondrial toxicity and oxidative stress, DNA damage, impaired axonal transmission, and ion channel remodeling in peripheral nerves [5].

The physical, emotional, and social quality of life of CIPN patients have a direct relationship with the severity of CIPN clinical manifestations. Also, CIPN causes the disability of sufferers and imposes a greater financial burden. On average, the healthcare costs of patients with CIPN are higher compared to the control group [6]. Therapeutic agents that increase the risk of CIPN include taxanes, vinca alkaloids, platinum drugs, bortezomib, and thalidomide [1]. The prevalence of CIPN depends on the type of anticancer agent, so that the prevalence rate varies from 19 to 85% (8:9), and the highest prevalence is related to the use of platinum-based drugs (70-100%), followed by taxanes (11-

87%), thalidomide and its analogs (20-60%) and ixabepilone (60-65%) [7]. CIPN is more likely to occur in patients with age, diabetes, vitamin deficiencies, or peripheral neuropathy [1].

According to the ASCO and ESMO guidelines, there are no effective or recommended agents for the prevention of CIPN. Based on the complex nature of CIPN, several treatment methods have been developed so far, some applicable therapies include Nerve-protective therapy, Ion channel-targeted therapies, Anti-inflammatory therapies, Neurotransmitter-based therapy, Antioxidants, Topical treatments, and Non-drug treatments [8].

Ozone therapy is the use of medical ozone as a therapeutic agent in pathologies with chronic hypoxia, inflammation, and redox imbalance. Medical ozone is a mixture of oxygen and ozone [9]. Ozone reacts with interstitial fluids producing hydrogen peroxide, aldehydes, and lipid oxidation products. These substances induce the activation of the NRF2 pathway, which itself induces an increase in antioxidant systems [10]. The activity of NRF2 leads to a decrease in the activity of the NFKB pathway, which induces an anti-inflammatory effect. By inhibiting the NF-kB pathway, the activity of proteolytic enzymes is also inhibited. Medical ozone has beneficial effects on the ability to modulate the redox balance, the state of cellular inflammation, and adaptation to ischemia/reperfusion processes [9]. From a clinical point of view, ozone therapy has multiple applications that are related to the germicidal capacity of ozone, inflammatory processes and chronic ischemia, and the imbalance of cellular redox status [11]. Considering that some of these processes play an important role in the pathophysiology of CIPN, ozone therapy can be effective in treating pain caused by CIPN.

Case report

The patient is 46 years old male with a history of metastatic cardia adenocarcinoma, treated with the drug regimen include alvoter, oxaliplatin, flurouracil. The patient presented with severe peripheral pain in the limbs, which was diagnosed as CIPN. The patient's pain level was estimated using the NRS scale at the beginning of the treatment period (NRS score of 10). He was treated with oxycodone 60-100 mg/day for 6-month but severity of pain did not change.

The treatment course included ten sessions of systemic ozone therapy using a new method, during which 60 cc of ozone with a dose of 50 µg/cc in 300 cc of sodium chloride 0.9% was administered intravenously for one hour on the first day and then during ten days, 10 cc was added to the volume of ozone mixture daily until it reached a dose of 100 cc with a concentration of 50 µg/cc on the fifth day, and then it continued with the same dose until the tenth day. The patient was under close respiratory and cardiac monitoring during drug administration. In addition to the above treatment, 30 mg/day duloxetine tablet, 300 mg/day vitamin B1 tablet were prescribed.

After five treatment sessions, pain level decreased from 10 to 5. The measurement of the patient's pain level showed that during ten sessions the pain score decreased from ten to about three. This case showed the efficacy of new systemic ozone therapy for pain treatment raised by CIPN.

Discussion and conclusion

There are three main ways of applying ozone in medicine: Topical, infiltrative, and systemic. Systemic ozone therapy consists of a mixture of gases that are mainly administered in two ways: the indirect intravenous route, known as autohemotherapy, and rectal enema.

The autohemotherapy method consists of extracting a certain amount of blood that is placed in a closed circuit. This blood is placed in contact with the gas in which it is dissolved and reacts in a few seconds and is immediately reinfused. This process requires certified medical devices. Another method is a rectal enema, which consists of administering a gas enema with a probe into the rectum. The gas in the rectum reacts with the mucosa and produces peroxides, which are absorbed by the mucosa and eventually enter the bloodstream. This process also requires certified equipment and the probe must be made of silicone or ozone-resistant plastics [9].

Several authors have reported the anti-inflammatory, analgesic, and anti-edematous properties of injected ozone and have suggested that oxidation of allogenic receptors inhibits the pain signal and activates the antinociceptive system [12]. There is also a report that the expression of pro-inflammatory, pro-apoptotic genes including caspases 1, 8, and 12,which that responsible for allodynia, is normalized due to peripheral injection of ozone gas mixture [13].

Ozone therapy has been identified as an adjunctive treatment for diseases associated with cellular redox imbalance or tissue oxygenation. This medication can help patients with chronic pain. There are observations that inflammatory and neuropathic pain caused by increased ROS can be reduced by systemic administration of a ROS-neutralizing agent. The role of ROS in hyperalgesia is exerted through the activation of NMDA receptors, and the analgesic effects of ozone occur by blocking the phosphorylation of NMDA [14].

Systemic ozone improves pain and the frequency of crises. The use of systemic ozone therapy improves efficiency and reduces the side effects of methotrexate in patients with rheumatoid arthritis [15]. Systemic ozone therapy has reduced interleukin 1 beta levels, which is directly related to disease activity [9]. The beneficial effects of systemic ozone therapy on pain reduction have been reported and several mechanisms have been suggested for it. However, the risks associated with direct gas injection to patients are one of the problems of its widespread use.

In the current report, the patient's pain was significantly reduced by the administration of half-saline ozone in a new way during the treatment period. In addition, the new innovative method has advantages such as the possibility of cost-effective indirect ozone injection to patients, which eliminates the need for certified devices. The innovative formulation is designed to minimize the possibility of blood pressure in patients and also reduce the risk of embolism. The indirect injection of ozone in this method is to reduce the risk of embolism, and therefore the solution is prepared by injecting ozone gas in a half-saline solution (0.45% sodium chloride) to prevent blood pressure increase.

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