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## Application of ozone therapy in interventional medicine

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## ABSTRACT

Ozone therapy has been gradually accepted by doctors in various fields because it has been safe, convenient, and inexpensive since the twentieth century. It has been used in the treatment of various diseases with satisfactory results, especially in the application of interventional surgery. For lumbar disc herniation, knee osteoarthritis, tissue ischemia-reperfusion after revascularization, stroke, and cancer, ozone therapy can improve the efficacy of interventional surgery and reduce postoperative acute and chronic complications. Prospects of ozone therapy in interventional therapy and the underlying mechanisms of efficacy need further exploration.

Ozone is an unstable gas comprising three oxygen atoms, and it is more soluble in water than oxygen. Ozone was used in medicine initially in the early twentieth century. Early on, it was used to treat gangrene in the wounded during the First World War. After the war, it was applied in wound disinfection, wound healing, hepatitis, arthritis, lumbar disc herniation, and other diseases. Doctors often achieved satisfactory effects. Ozone therapy has gradually become accepted as a non-traditional treatment because of its safety, convenience, low cost, and other advantages.<sup>1</sup>

## 1. Lumbar disc herniation

Low back pain is a very common disorder with significant impact on patients' clinical status. It is the fifth most prevalent condition that is treated in the world. The prevalence is estimated at 22–65% per year, and 90% of adults have had low back pain symptoms during their lives.<sup>2,3</sup> The management of low back pain should always start with a conservative approach; however, when this fails, minimally invasive techniques should be adopted before invasive surgery.<sup>4</sup>

Intervertebral disc and peripheral nerve root ozone injection has become a common treatment for herniated discs. It is widely prescribed in various countries of Europe, Asia, and South America; more than 600 treatments are performed every day in China alone.<sup>5,6</sup> Intervertebral disc ozone injections are the most common treatment, followed by injection around the nerve root.<sup>8</sup> Intra-disc injection of ozone can be considered for refractory discogenic sciatica for short and medium term pain in patients and is a minimally invasive, safe, and effective treatment.<sup>7–10</sup>

Most of the treatment is conducted under the digital subtraction angiography (DSA) with different ozone gas concentrations of 25, 30, 40  $\mu\text{g}/\text{ml}$ .<sup>3,11,12</sup> A small amount can be administered under the guidance of computed tomography (CT).<sup>8,13</sup> We typically use 35  $\mu\text{g}/\text{ml}$ , and there were no significant differences among these concentrations.<sup>14</sup>

There have been some new developments for the ozone therapy of lumbar disc herniation in recent years. Studies have shown that the patients with ozone injection monotherapy have marked pain relief, and the degree of mitigation is greater than that achieved with more conservative medical treatment.<sup>15</sup> Clinical trials have confirmed that its efficacy is better than laser disc decompression.<sup>12</sup> Furthermore, ozone monotherapy showed no significant difference with ozone + betamethasone combination therapy in postoperative pain relief, which suggests that ozone has excellent performance in pain relief.<sup>10,16</sup> By comparing the effects of ozone injection and the emerging Souchard's global postural re-education (GPR), it was confirmed that ozone ablation is better than GPR, and maintains long-term efficacy.<sup>17</sup> For the patients with lumbar disc herniation, ozone therapy can reduce the pain caused by nerve root compression and inflammatory stimulation, and have better prevention effects for motor weakness caused by nerve root symptoms. Ozone treatment substantially mitigates symptoms of motor weakness.<sup>7</sup> Clinicians have also used ozone injection combined with radiofrequency ablation of intervertebral disc. Although the combination did not show a clear advantage over radiofrequency ablation alone one month later, according to the one-year follow-up results, combination therapy has a stronger effect in alleviating pain than radiofrequency ablation alone.<sup>18</sup> A magnetic resonance imaging (MRI) T2 weighted image (T2WI) can be

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used to evaluate the efficacy of intervertebral disc ozone therapy.<sup>19</sup>

After years of exploration, some mechanisms of ozone treatment of lumbar disc herniation have been elucidated. Ozone not only inhibits local inflammatory response and alleviates hypoxia symptoms, but also damages muopolysaccharide chains in the nucleus pulposus and reduces its water content, resulting in a reduction in the size of the nucleus pulposus (which has been confirmed by CT and MRI T2WI<sup>13</sup>), which can mitigate the symptoms of pressure and stimulate fibroblast proliferation. Therefore, ozone therapy contributes to repair<sup>20</sup> and restores the patient's overall oxidative stress balance.<sup>21</sup>

The analgesic mechanism induced by O<sub>3</sub> may involve two independent steps: a short-term mechanism that may correspond with the direct oxidation of biomolecules and a long-term mechanism that may involve the activation of antioxidant pathways. Further studies are needed to support the biochemical analgesic mechanism of O<sub>3</sub> therapy.<sup>22</sup>

## 2. Knee osteoarthritis

Knee osteoarthritis (KOA) is a common disease, imposing a great burden through pain and decreased function. Numerous methods have been tested for pain management in KOA, and the optimal method is currently still under debate. Intra-articular injection of hyaluronic acid (HA) was associated with a significant reduction in visual analog scale score at 1 month compared to oxygen-ozone.<sup>23</sup> However, intra-articular ozone injections after arthroscopic surgery may effectively improve the outcomes of arthroscopic surgery in terms of pain relief, functional improvement, and quality of life in patients with KOA of Kellgren-Lawrence grade II or III.<sup>24</sup> Intra-articular injection of ozone plus oral celecoxib and glucosamine significantly decreased pain intensity in patients with mild to moderate KOA and improved their functional status sooner than oral celecoxib and glucosamine alone.<sup>25</sup> The combination of O<sub>2</sub>-O<sub>3</sub> and HA treatment led to significantly better outcomes compared to HA and O<sub>2</sub>-O<sub>3</sub> given separately to patients affected by KOA.<sup>26</sup> Intra-articular injection has not changed the serum concentrations of TNF- $\alpha$ , TNFR I, and TNFR II, but their synovial concentrations showed significant changes; the synovial TNFR I was significantly higher.<sup>27</sup>

## 3. Tissue ischemia-reperfusion

In peripheral, craniocerebral, and cardiac interventional procedures, we often encounter vascular occlusions that require us to perform complex re-operations, such as catheter embolization, balloon dilatation, and stent implantation. However, the ischemia-reperfusion injury that occurs after successful operation on the blood vessels in our surgery is problematic. How can we better reduce the impact of ischemia-reperfusion injury on the limbs or organs of patients?

Ozone is a strongly oxidizing gas, early experiments found that it can activate the body's oxidative stress defense system, stimulate the expression of nuclear factor erythroid 2-related factor 2 (Nrf2)/electrophile-responsive element (EpRE) by activating extracellularly regulated protein kinases and P38. Ozone can also promote the activity of superoxide dismutase and catalase.<sup>28–30</sup> Autohemotherapy, a treatment of disease by modification (as by ozone) of the patient's own blood, not only reduces the blood creatinine and urea nitrogen concentration from renal ischemia-reperfusion, but also protects the kidney tissue structure. Previously, it was thought that ozone regulated the NO pathway. However, now the hypothesis is that ozone stimulates increases in local  $\beta$ -NADPH-lipoamide dehydrogenase concentration. Autohemotherapy of human umbilical vein endothelial cells significantly increases both the rate of oxygen consumption and the mitochondrial activity as assessed by confocal microscopy.<sup>31</sup> Subsequent studies have shown that ozone modulates the accumulation of local neutrophils, the expression of IL-6, TNF- $\alpha$ , and ischemia-modified albumin in the kidneys and increases the total local antioxidant capacity.<sup>32</sup> Ozone therapy protects the tissue by reducing creatine kinase, aspartate aminotransferase, and K<sup>+</sup> ions in the muscle,<sup>33,34</sup> and decreasing mitochondrial damage caused by

ischemia-reperfusion injury (IRI). Ozone also inhibited the release of cytochrome-c from the mitochondria to the cytoplasm in SH-SY5Y cells. Apoptosis caused by IRI was inhibited by ozone, and ozone decreased apoptosis by increasing the ratio of Bcl-2/Bax and inhibiting the caspase signaling pathway in SH-SY5Y cells.<sup>35</sup> Ozone also prevented the elevation of blood urea nitrogen and creatinine, renal damage, and pyroptosis. Oxidative stress and pyroptosis were increased in the hypoxia and reoxygenation (H/R) model using NRK-52E cells.<sup>36</sup> Ozone oxidative preconditioning increased the expression of Nrf2 and decreased the levels of nucleotide-binding domain, leucine-rich repeat family pyrin domain-containing 3 (NLRP3), apoptosis-associated speck-like protein containing a caspase activation and recruitment domain (ASC), un-cleavable cysteine-requiring aspartate protease-1 (procaspase-1), cysteine-requiring aspartate protease-1 (caspase-1), and interleukin-1 $\beta$  (IL-1 $\beta$ ),<sup>37</sup> and increased antioxidant capacity and to protect the myocardium and lung against IRI.<sup>38</sup> A study about major ozonated autohemotherapy (MOA) showed that it attenuated renal IRI in rabbits shows that oxidative stress, neutrophil to lymphocyte ratio (NLR), interleukin-6 (IL-6), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), ischemia-modified albumin (IMA), total antioxidant status (TAS), total oxidant status (TOS), and oxidative stress index (OSI) have been increased.<sup>39</sup> Intestinal ischemia-reperfusion injury is associated with mucosal damage and has a high rate of mortality. Ozone therapy prevented IRI by mitigating IR-associated tissue injury.<sup>40</sup>

## 4. Stroke

Stroke is the second leading cause of death and disability in the world. Neurointervention has gradually become one of the main treatments in stroke treatment, but postoperative sequelae are still an urgent problem. Major ozonated autohemotherapy treatment in patients with acute cerebral infarction shows satisfactory results. It maintains ATP and energy metabolism in cerebral ischemia and hypoxia, and reduces cell apoptosis.<sup>41</sup> Doctors from Guangzhou General Hospital of Guangzhou Military Command assessed the outcomes according to the U.S. National Institutes of Health Stroke Score, Modified Rankin Scale, and transcranial magnetic stimulation motor-evoked potential. Major ozonated autohemotherapy may promote motor function recovery of the upper limb in patients with acute cerebral infarction.<sup>42</sup> Reduced degree of fractional anisotropy values of brain magnetic resonance diffusion tensor imaging were remarkably decreased, and brain function improved.<sup>43</sup> Therefore, it is a good choice to give ozone treatment after stroke.

## 5. Cancer

Tumor treatment is a difficult problem. The best known interventions for tumors are surgery, which is highly invasive, and chemotherapy, which has intense side effects. In recent years, interventional therapy has become an indispensable treatment method due to minimal invasiveness and side effects. Ozone treatment has shown excellent auxiliary effects in cancer treatment. It is not only effective against papillomavirus-induced lesions, particularly against those induced by the most common high-risk virus, HPV16,<sup>44</sup> but also a valid supportive therapy for fatigue in cancer patients, both during cancer therapy and in a palliative setting with no significant side effects.<sup>45</sup> Ozone could be useful in colon cancer management in combination with 5-fluorouracil and cisplatin by significantly inhibiting cytokines that have a central role in colon cancer cell survival and chemoresistance.<sup>46</sup> The use of ozone therapy in these patients enhances the action of chemotherapy and at the same time reduces side effects, such as nausea, vomiting, opportunistic infections, buccal ulcers, hair loss, and fatigue. Such positive therapeutic effects of ozone therapy can improve broader physical and mental wellbeing, resulting in improved quality of life.<sup>47</sup>

Ozone can also prevent side effects of some chemotherapy drugs, such as preventing doxorubicin-induced dilated cardiomyopathy through an increase of antioxidant enzymes and a reduction of oxidized

macromolecules.<sup>48</sup> Preconditioning and treatment with ozone attenuated the nephrotoxicity induced by methotrexate in rats by activating anti-oxidant enzymes and preventing renal tissue damage.<sup>49</sup> In addition, some scholars have applied ozonated saline to treat VX2 tumors. Ozonated saline at 20 µg/mL and 40 µg/mL were directly injected into the tumors respectively (injection volume = 1/2 volume of the tumor); tumor-growth was controlled in the near term,<sup>50</sup> but due to the production of sodium hypochlorite in ozonated saline, long-term use may cause cancer. Therefore, it is not recommended for clinical application.

In summary, ozone therapy, like interventional therapy, is a new treatment in the long history of human medicine, and it needs further exploration and research. Ozone is currently used in a wide range of interventional therapies. It can help interventionalists achieve better results in the treatment of various diseases.

### Conflicts of interest

The authors declare that they have no conflicts of interest.

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### Informed consent

Not applicable.

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