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ABOUT COVER

Editor-in-Chief of *World Journal of Clinical Cases*, Bao-Gan Peng, MD, PhD, is Professor and Director of the Department of Orthopedics at The Third Medical Center of PLA General Hospital. Professor Peng's research interest is spinal surgery. His career work has generated a multitude of new academic viewpoints and theories, and more than 200 academic papers, published both at home and abroad. In practice, he has systematically elucidated the pathogenesis of discogenic low back pain and established a new minimally invasive treatment method: The intradiscal methylene blue injection. He also revealed and characterized a new pathogenesis of Schmorl's nodes, which is a now a famous concept. Finally, he was the first to discover that ingrowth of Ruffini corpuscles into degenerative cervical disc is related to dizziness of cervical origin. (L-Editor: Filipodia)

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WJCC mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

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Expert consensus of Chinese Association for the Study of Pain on the application of ozone therapy in pain medicine

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Abstract

This consensus was compiled by first-line clinical experts in the field of pain medicine and was organized by the Chinese Association for the Study of Pain. To reach this consensus, we consulted a wide range of opinions and conducted in-depth discussions on the mechanism, indications, contraindications, operational specifications and adverse reactions of ozone iatrotechnique in the treatment of pain disorders. We also referred to related previous preclinical and clinical studies published in recent years worldwide. The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications in this process.

Key Words: Ozone iatrotechnique; Pain department; Expert consensus; Pain; Ozone; Guideline

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Core Tip: We consulted a wide range of opinions and conducted in-depth discussions on the mechanism, indications, contraindications, operational specifications and adverse reactions of ozone iatrotechnique in the treatment of pain diseases. We also referred to the related previous preclinical and clinical studies published in recent years around the world. The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications in this process.

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INTRODUCTION

Ozone is a strong oxidant and can be used in the treatment of pain disorders due to a variety of significant biological effects in the body^[1]. Since 2002 in the Pain Department of hospitals in China, ozone has been used in the therapy of some disorders, including degenerative spinal diseases, musculoskeletal disorders and diseases, rheumatic immune diseases, vascular diseases, metabolic diseases, neuropathic pain, *etc*^[1-4]. There is a lack of uniform norms and guidelines in clinical practice due to the unreasonable application of ozone from time to time. Some adverse reactions and complications, such as injections into blood vessels or cerebrospinal fluid, have been observed. In order to standardize the rational application of ozone treatment technology in the pain clinic, improve the therapeutic effect and prevent and reduce the occurrence of adverse reactions, first-line clinical experts in the field of pain medicine in China were organized by the Chinese Association for the Study of Pain to assess and discuss the mechanism, indications, contraindications, operating norms and adverse reactions of

ozone in the therapy of pain disorders. The China Expert Consensus on the Application of Ozone Therapy in the Pain Department was reached by assessing the topics discussed below.

PHARMACOLOGICAL MECHANISMS

Under the appropriate ozone concentration, biochemical reactions similar to preadaptation are produced in the body's cells^[5]. There are no ozone receptors in the human body. Therefore, the pharmacological mechanism of ozone is indirectly realized through other factors.

Ozone has a well-known analgesic effect. Subcutaneous injection of ozone at painful area quickly inactivates the inflammatory factors, reduces the stimulation of inflammatory factors to sensory nerve endings and inhibits peripheral sensitization thereby producing its analgesic effects^[6]. In addition, direct stimulation to sensory nerve endings by ozone can induce the activation of endorphins in the nervous system thus inhibiting the transmission of peripheral injurious stimulation signals to the advanced center^[7]. Ozone administered *via* the transforaminal route also stimulates inhibitory interneurons to release enkephalin and other substances thereby achieving central analgesia^[8]. This type of analgesia occurs quickly after injection. This may be the molecular mechanism of rapid analgesia following ozone administration.

An endogenous antioxidant system can be initiated by ozone therapy (ozone autohemotherapy or tissue injection) by a variety of methods. The expression of heme oxygenase-1 in the local microenvironment is increased, and antioxidation is activated through heme oxygenase-1-mediated signaling to downstream targets^[9]. The expression of superoxide dismutase is stimulated further decomposing excess peroxidation free radicals. Catalase is generated, and hydrogen peroxide is decomposed. The synthesis of glutathione peroxidase is increased, and organic peroxides are decomposed. Furthermore, the level of glucose-6-phosphate-dehydrogenase is increased in pentose phosphate bypass metabolism enhancing the antioxidant reduction ability of nicotinamide adenine dinucleotide phosphate^[10]. Due to the effect of ozone, the body's active removal of free radicals and peroxides generated in the microenvironment as a result of physiological and pathological processes is accelerated.

Ozone has immunomodulatory and anti-inflammatory effects^[8,11,12]. Peripheral sensitization caused by inflammation is the core factor in pain^[13]. Ozone autohemotherapy or tissue injection have immune enhancement effects, such as enhancing phagocytic function of granulocytes and macrophages and improving the body's removal of pathogenic microorganisms or metabolic waste. On the one hand, it inhibits the synthesis of proinflammatory cytokines by inhibiting nuclear transcription factors, such as nuclear factor kappa-B^[14]. On the other hand, it increases the synthesis and release of anti-inflammatory cytokines leading to the rapid elimination of inflammation^[15]. Local tissue injection of ozone can increase oxygen supply, improve tissue hypoxia and act as a free radical scavenger. Ozone can be quickly reduced to oxygen after exposure to the surface of reductive cells creating an oxygen-rich environment in the local area. Stimulation of ozone affects vascular endothelial cells, which can release nitric oxide and other substances, dilate blood vessels to improve local microcirculation and thus stimulate tissue repair^[16].

The effect of ozone on bidirectional regulation of immunity is also manifested in the induction of immune cells to produce massive amounts of cytokines. Ozone autohemotherapy can lead to a small release of interferon- γ , interferon- β , tumor necrosis factor α and granulocyte-monocyte colony stimulating factor in human blood^[17-19]. These cytokines have multiple effects, such as immunostimulation or immunosuppression. The excessive use of ozone has a bidirectional regulation effect even on immunosuppression^[20,21]. Therefore, different ozone concentrations and courses have different regulation methods and effects on the immunologic function of the body.

It should be noted that taken together, the functions of immunoregulation and antioxidation are achieved by triggering the body's endogenous protective mechanism. However, the buffering ability of the body's endogenous protection mechanism is limited. There are also great differences in the buffer capacity and repair capacity of different tissues and cell types. Ozone overdose within a short time may exceed the body's buffer capacity leading to reduced immune function, oxidative damage and adverse reactions. Therefore, it is necessary to strictly control the application of ozone concentration and total capacity. Indications and contra-

indications should be strictly observed.

INDICATIONS AND CONTRAINDICATIONS

Indications for ozone therapy are as follows: (1) Neuropathic pain: Herpes, postherpetic neuralgia and central pain^[22], syringomyelia, diabetic peripheral neuropathy^[23] and central and peripheral nerve injury pain^[24]; (2) Vasogenic pain: diabetes and peripheral vascular disease^[25], thrombotic ischemic pain^[3,26,27], Raynaud's disease, erythromelalgia and vasculitis^[28-30]; (3) Metabolic immune diseases: Ankylosing spondylitis, rheumatoid arthritis^[31], allergic diseases and gout^[32,33]; (4) Infectious diseases: Necrotizing ulcers, hard to heal wounds^[34,35] and burns; (5) Physiological pain: Dysmenorrhea; (6) Tumor pain: Tumor pain during adjuvant therapy, radiotherapy and chemotherapy side effects, tumor consumption treatment and cancerous neuralgia^[36]; and (7) Degenerative spinal diseases and joint and skeletal muscle diseases: Discogenic low back pain, lumbar disc herniation, cervical spondylosis, knee osteoarthritis, hip osteoarthritis and pain caused by chronic muscle, tendon, ligament, fascia and joint capsule strain^[37].

Contraindications to ozone therapy are as follows^[38]: (1) Ozone allergy; (2) Favism (glucose-6-phosphate-dehydrogenase deficiency); (3) Pregnant women; (4) Hyperthyroidism; (5) Sickle cell anemia; (6) Patients receiving kinase anticoagulant drugs; (7) Severe arrhythmia, hypertensive crisis and other cardiovascular diseases; (8) Hemochromatosis and patients receiving copper or iron therapy; and (9) Other relative contraindications (myocardial infarction, hypotension, hypocalcemia, hypoglycemia, internal hemorrhage, thrombocytopenia, coagulopathy, acute alcoholism and citrus allergy).

COMMONLY USED INJECTION CONCENTRATIONS, CAPACITY, TREATMENT AND OPERATION SPECIFICATIONS

Several forms of ozone are used in the treatment of pain. Ozone gas is easily decomposed at room temperature and pressure, is very unstable and can decompose into oxygen. It cannot be stored. On-site production is commonly used for immediate application. Ozone water is an ozone gas under a saturated state dissolved in a distilled water solution. Different to ozone gas, it is still a strong oxidation agent. In clinical medicine, ozone water is mainly used for local anti-inflammatory treatment, infection wound treatment and pelvic inflammatory disease treatment. Ozone oil is a mixture of ozone dissolved in a medical-grade greasy substance. Ozone in the oil is slowly released during use. Clinically, it is mainly used in the treatment of diseases of the mucous membranes, including diabetic foot, atopic dermatitis and chronic ulcer.

In clinical application, differences in the ozone concentration and capacity are significant over time relying mainly on the experience of physicians^[39]. The ozone concentration is divided into the following three categories based on the method and mechanism of clinical application of ozone: High concentration (50-80 µg/mL); medium concentration (30-50 µg/mL); and low concentration (10-30 µg/mL). The oxidation capacity is increased with the rise in concentration^[4]. The amount of ozone in the same area of different patients should be adjusted according to their tolerance, individual differences and other factors. Generally speaking, the concentration for intervertebral disc injection is 40 µg/mL, no greater than 30 µg/mL in other parts of the intervertebral disc and no greater than 45 µg/mL in autologous blood. In addition to air bath therapy, high-concentration therapy is not recommended.

The capacity of ozone injection is related to the therapeutic target, as described below: (1) Intra-articular injection^[40]: It is recommended that intra-articular injection should be performed under X-ray/ultrasound positioning to ensure the injection of ozone into the joint cavity. According to the capacity, the joint cavity of the human body can be divided into large joints (shoulders, knees, hips), medium joints (skull) and small joints (elbows and wrists). The recommended standard for intra-articular injection of ozone is shown in Table 1; (2) Injection around the joint: Ozone is accurately injected into the pain points around lesions, the tendons and ligaments. The recommended ozone injection concentration is no greater than 30 µg/mL, and capacity is 1-5 mL/site. The total amount during a course of treatment is no greater than 30 mL with a frequency of 1-3 times/wk. The treatment course is 2-4 wk. Commonly used joint injection sites are around shoulder joints including coracoid sites, large and small

Table 1 Intra-articular injection and treatment

Target	Concentration, µg/mL	Capacity, mL	Frequency, times/wk	Course of treatment, wk
Large joint	< 30	10-20	1-2	2-4
Medium joint	< 30	5-10	1-2	2-4
Small joint	< 30	1-5	1-2	2-4

nodules of the humerus, intertubercular sulcus, sites below the acromion, the insertion point of the triangular muscle, the superior angle and inner corner of the scapula, the upper part of spinae scapulae and the lower part of spinae scapulae. Usually, 3-5 injection points are selected for each injection and include the lateral collateral ligament attachment sites, the suprapatellar bursa and infrapatellar bursa, fat pad sites, tubercles of the tibia and other painful areas; (3) Injection of soft tissue at pain points: The most obvious area of tenderness is selected for injection. It is recommended that the myofascial trigger points are located under the guidance of B-scan ultrasonography. The recommended ozone injection concentration is no greater than 30 µg/mL, capacity of 1-5 mL/site at a frequency of 1-3 times/wk and a treatment course of 2-4 wk. The total amount during treatment is no greater than 30 mL; (4) Injection around the nerve roots: Transforaminal injection, epidural steroid injection and interlaminar epidural injection are widely used to treat nerve root pain caused by diseases such as disc herniation. Bonetti *et al.*^[41] used 25 µg/mL ozone for transforaminal injection into the epidural space and achieved good results in the treatment of low back pain. In addition, other studies have confirmed the effectiveness of concentrations of 10 µg/mL and 20 µg/mL. Therefore, the recommended concentration for ozone injection of the epidural space is 10-30 µg/mL through various access points. The recommended volume is 3-5 mL for the cervical segment, 5-10 mL for the thoracic segment and 10-20 mL for the lumbar segment with a frequency of 1-3 times/wk. The course of treatment is 2-4 wk. It is recommended that this should be performed under the guidance of X-ray, nerve stimulator and ultrasound. If necessary, angiography can be performed to locate the puncture site. Local anesthetic testing should be performed to ensure the integrity of the dura mater before injection. The injection speed should be slow with the aim of obtaining a more precise curative effect and to ensure safety; and (5) Intradermal injection: This is mainly used for the treatment of herpes zoster and postherpetic neuralgia. The specific operation is as follows. An injection point on the skin in the painful area is selected. The ozone concentration for injection is 20 µg/mL. After injection, an orange peel-like ridge of less than 1 cm is formed at each point. The point-to-point distance is approximately 1 cm, forming a network arrangement. Injection is performed once every other day, 2-3 times a week.

Operation specifications are as follows. The injection should be implemented according to the relevant operation specifications shown in the Clinical Practices-Pain Science Volume published by the Chinese Medical Association. The injection should be performed under strict aseptic conditions. It is recommended that the accurate position should be achieved under imaging guidance. If necessary, angiography can be performed to locate the puncture position. Vital signs should be monitored to prevent the occurrence of adverse reactions.

OZONE INJECTION ABLATION FOR THE TREATMENT OF INTER-VERTEBRAL DISC DISEASES

Ozone has been proven to cause dehydration of the nucleus pulposus^[42,43]. Therefore, the injection of ozone into the intervertebral disc can reduce the lesion volume of the intervertebral disc and help alleviate the compression on nerve roots^[44,45]. More importantly, ozone has a good anti-inflammatory effect, which is conducive to reducing inflammation of the intervertebral disc, nerve roots, ganglia and surrounding tissues.

Indications include patients with disc herniation who have similar clinical symptoms, signs and imaging findings. Contraindications include issues with ozone application and in patients receiving lumbar puncture.

Ozone ablation in the treatment of herniated lumbar intervertebral disc should be performed in a sterile environment and monitored by imaging. Patients should be

informed of all the potential risks and benefits of treatment and have signed an informed consent before treatment.

The concentration for ozone ablation in the treatment of herniated lumbar intervertebral disc is usually 40 µg/mL^[46,47]. The capacity of each lumbar spine disc is 4-5 mL^[46], and the capacity of each cervical spine disc is 2-3 mL. The injection rate should be slow, and the patient's response should be observed throughout. Although intervertebral disc ablation is effective after only one treatment, it can be repeated several weeks or months later.

PREVENTION AND TREATMENT OF ADVERSE REACTIONS AND COMPLICATIONS

Allergic reaction is a common side effect. If patients suffer diffuse erythema, rash and itching, it is usually considered an allergic reaction. No further risks and complications have been noted.

OZONE AUTOLOGOUS BLOOD THERAPY

Ozone autologous blood transfusion therapy (hereafter referred to as "autologous blood"), also known as ozone immunotherapy, involves an appropriate concentration and volume of ozone used to treat a certain amount of blood extracted from the patient's body. Then the blood is reinfused into the patient's body in an effort to obtain clinical efficacy. It includes large autologous blood therapy and small autologous blood therapy^[1]. In large autologous blood therapy, a total of 100-150 mL of blood is obtained each time. It is then reinfused into venous blood vessels after treatment with an appropriate volume of ozone. In small autologous blood therapy, only 5-10 mL blood is obtained. After ozone treatment, intramuscular injection is performed, generally into the gluteus muscle^[48,49]. Large autologous blood therapy is mostly used during surgery.

Mechanism of the action of large autologous blood therapy

The mechanism of the action of large autologous blood therapy is unclear at present. Some studies have shown that ozone binding to blood effects the following aspects: (1) Activates erythrocyte metabolism, increases the oxygen saturation of hemoglobin and enhances the application of oxygen and adenosine triphosphate in tissues. It improves oxygen supply, promotes blood circulation, enhances cell vitality and repairs tissue cells; (2) Regulates the body's immune system. It enhances the phagocytic function of granulocytes and macrophages, improves the body's ability to remove metabolic waste and accelerates the removal of germs, viruses, *etc.*; and (3) Activates the antioxidant enzyme system, removes lipids from the blood and metabolic waste, enhances the activity of antioxidant enzymes in the body and reduces the damage caused by free radicals in the body^[14]. It improves blood viscosity, reduces blood glucose, uric acid, bilirubin, lactic acid and pyruvate, strengthens the decomposition of cholesterol and triglycerides, improves the status of vascular walls and prevents systemic atherosclerosis and neurological lesions^[50].

Equipment and large autologous blood therapy procedure

The large autologous blood treatment room should be a well-ventilated, air-disinfected independent treatment space with an average area greater than 20 square meters *per* treatment bed.

Preparation before treatment

The windows (doors) of the treatment room are opened for ventilation. The power supply, oxygen cylinder and interface connection are checked. The oxygen cylinder switch is opened. The oxygen pressure is checked to make sure there is no air leakage. The power switch of the ozone generator is turned on. The supplies are checked: Special package for basic autologous blood therapy, a bottle of 150 mL saline and treatment vehicle (tourniquet, disinfection cotton swab and disinfectant).

Treatment

The patient is placed in the supine position. The middle vein of the patient's elbow is

selected for blood collection. The blood collected should be shaken slowly and evenly clockwise during blood collection, thereby blood and anticoagulants are fully mixed. A volume of 100-150 mL is often used for blood collection. The maximum volume is 200 mL. After the completion of blood collection, a certain concentration of ozone gas at the same volume is injected under aseptic collections. At the same time as ozone injection, the blood collected is slowly and evenly shaken clockwise, so that ozone and blood are fully mixed. The mixing time is approximately 3-4 min from the time of ozone injection, and then the blood is reinfused into the patient's body. Attention is paid to monitoring the patient at the time of reinfusion.

Courses and concentrations of large autologous blood therapy

In large autologous blood therapy, the course of treatment is generally 10-15 times. The treatment can be performed once a day or every other day. A course interval of more than 6 mo is recommended.

The concentration of ozone during large autologous blood treatment is usually increased from a low dose. The initial concentration is 20-30 µg/mL with an increment of 5 µg/mL. The concentration can be increased between the first and second therapy. The maximum concentration is no more than 45 µg/mL. The patient's treatment outcome and side effects need to be assessed before each increase in concentration to ensure safety.

Precautions

The whole process should be carried out under sterile conditions. Every operator should have a set of consumables (blood collector, blood harvesting and infusion tubes, ozone collectors, normal saline). The patient's condition should be closely observed during the operation process. If there is a problem, then it should be solved immediately. The amount of blood collected, ozone injection and ozone concentration should not be increased without authorization. Blood reinfusion should be slow. It is usually completed within 10-15 min. During the first treatment, it should be slowed down further to prevent complications, especially in elderly patients.

Side effects of large autologous blood therapy

There are few side effects of large autologous blood therapy. Patients may have a rash or other allergic reactions, which can be easily resolved. If necessary, symptomatic treatment can be performed. Some patients faint during venous puncture due to emotional stress. Anticoagulant allergy is manifested as a mild numbness of the lip and tip of the tongue, which can be relieved spontaneously. In addition, it can be solved by changing the anticoagulant. Some patients feel nauseous, and flatulence or mouth odor can occur. These symptoms can be relieved spontaneously.

In addition to the general introduction of ozone treatment indications, large autologous blood therapy is widely used in other treatments, including respiratory, digestive, neurological, endocrine and metabolic systemic diseases^[51-54].

EXPERT CONSENSUS STATEMENT

Ozone is a gaseous molecule with strong oxidation characteristics, which is widely used in the treatment of pain and related diseases.

The effects of ozone include analgesia, anti-inflammation, oxygen supply increase and bidirectional regulation of immunologic function.

Local ozone injection can be used in intradermal sites, skeletal muscle pain points, sites around the joint cavity, nerve roots, *etc.* The local injection concentration is no greater than 30 µg/mL. The total amount during each treatment is no greater than 30 mL. The course of treatment is determined according to the location.

Ozone injection can be used for the treatment of intervertebral disc diseases. For ozone injection ablation for the treatment of intervertebral disc diseases, 40 µg/mL is considered the commonly used concentration. The capacity of each lumbar spine disc is 4-5 mL, and the capacity of each cervical spine disc is 2-3 mL.

Indications, contraindications and operating norms should be strictly observed in ozone autologous blood therapy. Generally, 100-150 mL of blood is extracted, up to a maximum of 200 mL. The maximum ozone concentration is 45 µg/mL.

Ozone can also be used for adjuvant treatment of pain-related diseases.

Operators should comply with the consensus on ozone application indications, contraindications and use norms to ensure the safe application of ozone treatment technology.

CONCLUSION

The purpose of this consensus is to standardize the rational application of ozone iatrotechnique in pain treatment, to improve its efficacy and safety and to reduce and prevent adverse reactions and complications due to this process.

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