German Medical Association of Ozone Application in Prevention and Therapy

European Cooperation of Medical Ozone Societies

Member of the "European Cooperation of Medical Ozone Societies"

Guidelines for the Use of Ozone in Medicine

Medical Ozone as a Pharmaceutical Agent

Pharmaceuticals in the gaseous state are exceptional and special forms of application are required. In the case of medical ozone/oxygen mixtures, oxygen is not only used as a generator gas to produce the corresponding ozone mixture, but also, at the same time, as a solvent in the range from 0.05 to max. 5.0 vol% ozone, corresponding to the concentration range of 1.0 to 100 µg/ml ozone applied in practice.

Preparation and Measurement

Contrary to technical and smog ozone, the O_3 used in medicine is produced from pure medical oxygen via silent electrical discharge; it is not possible to use oxygen concentrators or oxygen/air mixtures due to their nitrogen component and the consequent possibility of nitrogen oxides being formed in the discharge tube.

As with other pharmaceuticals, medical ozone is a clearly defined molecule with a clearly defined range of action. With a half life of 55 minutes in a 50 ml disposable injection syringe (completely siliconized and ozone resistant), medical ozone must be prepared on site and made specially available for the type of application required.

As the concentration and decomposition rate of ozone is extremely dependent on different parameters such as temperature, pressure, volume flow rate etc., medical ozone generators have to be equipped with a measurement device to ensure continuous concentration control (Fig.1)

Ozone produced in excess, either as part of the generator gas or after local application, must always be completely reduced back to oxygen to avoid odour and inconvenience to the respiratory tract; correspondingly, the system must be equipped with high-power catalysts (due to temperature and burning risk active carbon must not be used). The maximum work place concentration is 200 µg/m^3 ; the max. immission concentration of 120 µg ozone/m^3 is cited for use within closed areas (WHO).

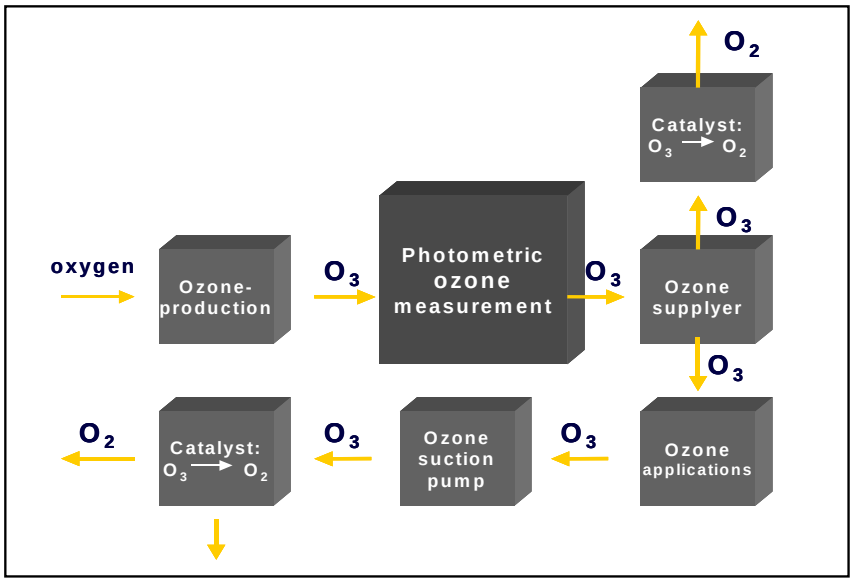


Figure 1: Processing of a medical ozone generator

Measuring Ozone

Due to a powerful absorption band near the ultraviolet range (Hartley Band) with a max. absorption at 254 nm, a photometric procedure is a method of choice at this wavelength for continuous ozone concentration measurement, and has become an international standard which other measuring methods make use of to orientate their values and correspondingly apply in calibration.

Quality Assurance

From a quality assurance and quality control point of view, the high reactivity of ozone with organic substances requires a careful selection of materials needed for the different types of medical equipment:

- Only special materials can be used in ozone generators, such as Teflon (PTFE), specially anodized aluminium (anti-friction), V4A-quality stainless steel (in long-term use, V2A quality is subject to surface changes), glass and ceramics
- For application systems only "ozone-resistant" materials such as glass, polyethylene (PE) ,polypropylene (PP) , and PTFE come into the question
- Other plastics, especially for syringe pistons, must be silicone-coated
- Medical plasma flasks as used for reinfusion should be made of glass only; the plasma bags made of soft PVC in general hospital use are NOT ozone-resistant.
- The use of plasma bags made of non-ozone-resistant, soft polyvinylchloride (PVC) is to be rejected. This is because reactions between the ozone and the plastic material can occur producing xenobiotic and/or toxic substances, especially during O_3 blood treatment requiring up to 5 minutes to obtain the proper effect. The substances arising from a decomposition of the softening agents in the plastic, such as e.g. hydrogen peroxide or phthalicacid esters are

not only able to distort the desired effects of ozone, but also damage the patient's health

- For preparing and storing ozonized water, containers made exclusively of glass are to be used, these having a small volume (e.g. 250 ml) as far as possible; they should be completely filled and well sealed [also with O_3-resistant material]
- Use sterile, siliconized, 50-ml disposable syringes (ozone half life: 55 min) to transport ozone/oxygen mixtures for use during home visits. See fig. 2-3.

Ozone generators as well as the disposables used for treatment have to fulfil the MDD (Medical Device Directives) in Europe (93/42 EC), are labelled with a CE sign including the number of the supervising authorities. The producers have to present the specific and valid certificates.

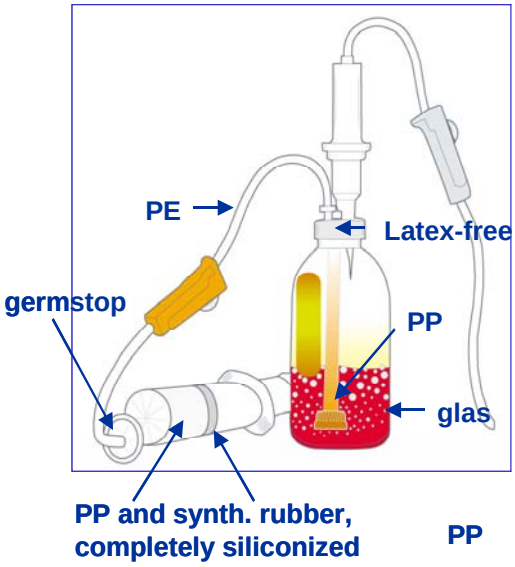


Fig. 2: Material for MAH

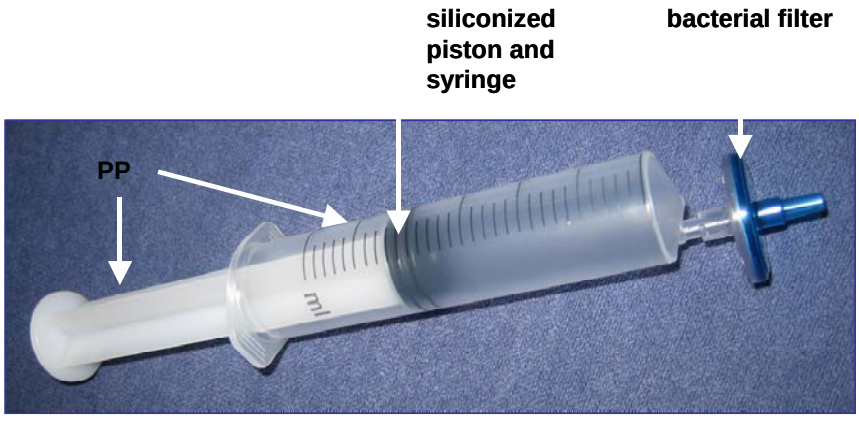


Fig. 3: Material for ozone injections (intra articular, intramuscular)

Therapeutic Application of Medical Ozone

Major Auto Haemotherapy MAH with Ozone as a Systemic Application

The drawing up of guidelines for quality assurance and the procedures for MAH is only useful if, right from the beginning, wrong applications are recognized as being quality detraction factors and have to be completely avoided, such as

1) the performance of intravenous injections and transfusions under pressure (which cause air embolisms),
2) the application of O_3 gas in the wrong kind of bag (use of non-ozone-resistant serum bags with subsequent formation of xenobiotic substances),
3) the withdrawal of an O_3/O_2 gas mixture via a direct and solid tube connection between the outlet valve of the generator and the flask (producing retrograde contamination with blood), or
4) the re-use of syringes a number of times without disinfecting, cleansing and sterilizing them as required.

Indications and Application Methods

MAH is reserved for special indications as complementary concept. These are:

Arterial circulatory disturbances
- peripheral arterial circulatory disturbance
- cerebral circulatory disturbance (stroke)
- ocular circulatory disturbances (retinopathies)
- inner ear circulatory disturbances (acute hearing loss (AHL), tinnitus)

Angiopathia
- esp. diabetic angiopathia

Virus-caused diseases
- hepatitis B and C
- herpes simplex, herpes zoster

General immune deficiency
- as complementary therapy in general weakness, geriatric, environmental medicine

Complementary concept in oncology.
Chronic inflammatory processes in orthopedics and rheumatology

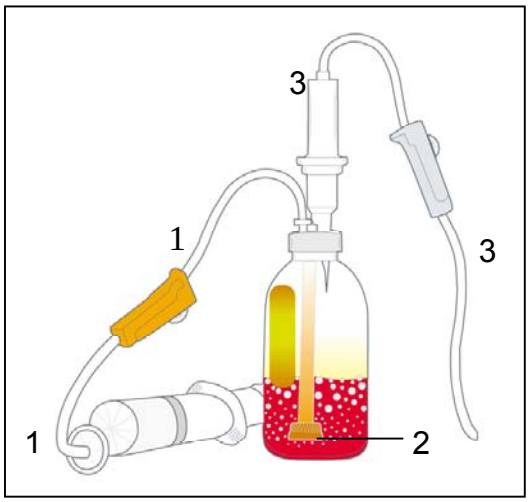
Contraindications

- Glucose-6-phosphate dehydrogenase deficiency (favism, acute haemolytic anaemia)
- Hyperthyroidism if not controlled
- Pregnancy in the
- first 3 months
- MAH is not indicated in leukaemia

Procedure

In MAH, under strict aseptic conditions, 50-100 ml venous blood are withdrawn from the patient and transferred to a vacuum flask with sodium citrate, where the medical ozone / oxygen gas mixture is added to it - extracorporeally in a closed, sterile and pressure-free system- before being retransfused via drip infusion (Fig.4, Tabs. 1 and 2). Technically, the “medical ozone" used is, in actual fact, a mixture of purest ozone and medical oxygen (0.05-5% (Vol.) ozone = 1-100 µg/ml ozone + 99.95-95% oxygen). By contrast to naturally occurring and anthropogenic, impure ozone, its quantity is exactly prescribed (10-40 µg ozone / ml blood).

The ozone/oxygen mixture must pass through the patient's blood evenly, preferably using what is called the microbubble system to produce a reaction surface as large as possible in the short reaction time (less than 1 second). Thus the ozone contact can take place with nearly all RBC´s and nearly all WBC´s making the ozone reaction as effective as possible, while the oxygen bubbles through, forming a layer of O_2 gas above the liquid level in the flask, fig 4.



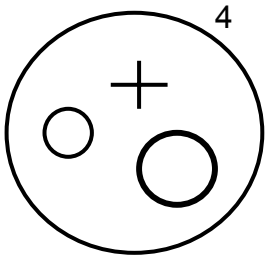


Fig. 4. MAH
1. “germstop” with bacterial filter
2. micro-bubble system
3. transfusion set
4. stopper, surface view

Following contact with the blood outside the body, not a single ozone molecule, and not a single oxygen molecule either, enters the patient's vascular system. Only the products of a reaction between the ozone and the cellular components of the blood, i.e. the non-radical ozone hydroperoxides are reintroduced. In the presence of organic substances, such as membrane lipids, the life of a highly reactive ozone molecule is extremely short (< 1 sec), i.e. it is reduced prior to re-transfusion.

- Hand disinfectants on an alcohol basis
- Skin disinfectants on an alcohol basis or sterile alcohol swabs vacuum-packed in plastic foil
- Sterile cotton wool or gauze swabs
- Hypoallergic injection plaster
- Sterilized covering cloth

Tab. 1. Preparation and performance of MAH - equipment required

- 250 ml sterile vacuum gas flask with microbubble system, with sterile, pyrogen-free sodium citrate, without preserving agents
- Sterile, pyrogen-free transfusion unit with gravity drip chamber and tube clamp
- Sterile, pyrogen-free butterfly (cannula) set
- Sterile, pyrogen-free "germ stop" type transfusion set with bacterial filter and tube clamp, for O_3 administration in the 250 ml sterile vacuum gas flask
- Sterile, silicone-coated 50 ml disposable syringe, with pre-connected bacterial filter
- Mobile (! Independent of patient) ozone supply unit (generator) equipped with a photometer for concentration measurement.

Tab. 1 cont.. Preparation and performance of MAH — equipment required

- Disinfect both hands properly using 3-5 ml of a special hand disinfectant, observing the prescribed time to take effect of at least 30 sec; in cases of possible contamination with stable viruses (HBV, HCV, HIV) this period should be 5 min. It is the aim of these elaborate precautions to encourage the wearing of protective (surgical) gloves, a preferable measure in all cases.
- Cover a suitable area with a sterile cloth for setting out the equipment described above (Tab. 1) once taken out of its packing, as necessary for treatment; then use a colour-marked, sterile cloth to prepare the entire system (as hygiene set if required)
- Remove the protective cap of the 250-ml vacuum flask; the preferable method is to use both thumbs, pushing up and away from below. Disinfect the stopper with a skin disinfectant by spraying on, allow to dry (requires > 1 min to take effect)
- Close clamps and introduce the cannula of the "germ stop" system through the cross marked on the stopper (microbubble system).
- Close clamp of the transfusion set, introduce it through the large circle marked on the stopper by piercing through.
- From the teflon adapter on the generator, withdraw the O_3/O_2 mixture with a sterile, silicone-coated 50 ml disposable syringe with a preconnected bacterial filter (after previous loosening the piston of the syringe to overcome possible adhesion). The syringe is filled by the inherent pressure in the unit. Flush out the syringe as required with the gas once more. The rest ozone is converted back to pure oxygen by the catalyst. In this way, neither the generator nor the syringe come directly into contact with the patient. Always remember that **dry** ozone is **not** able to act as a microbicides, inactivate viruses, or disinfect; so bacterial filter and syringe can only be used once.
- Connect the syringe filled with 50 ml gas mixture to the cone of the bacterial filter of the "germ stop" system
- Disinfect the patient's skin properly in the area round the infusion site (arm vein) by thorough wetting via spraying on a skin disinfectant and distributing it with a sterilized cotton swab or gauze (in vacuum pack); allow to take effect for at least 1 min. From the butterfly cannula, withdraw approx. 50 ml patient's blood via the infusion lead into the vacuum flask and fix butterfly with strip of plaster.
- Withdraw the O_3/O_2 mixture under vacuum from the disposable syringe via the bacterial filter of the "germ stop" system to ensure a smooth passage through the blood in the form of minute bubbles producing the desired immediate reaction between the ozone and blood cells. After passing through the blood, the remaining oxygen accumulates in the flask above the surface of the liquid
- Carefully turn over the vacuum flask, remove the gas syringe for de-aeration and pressure-free re-transfusion of the ozone-treated blood
- Remove the intravenous butterfly cannula, dab over the infusion point using a sterile cotton or gauze swab before covering it with a pressure dressing (hypoallergic injection plaster).

Tab. 2. Performing MAH, including aseptic procedures

Ozone Concentrations and Dosage in Reinfusion Treatment

Based on the results of fundamental research over the last 18 years, the ozone concentrations and required total amounts determined in practice can be given in concrete terms.
The concentrations used below are cited in the standard measuring unit of micro-grammes per millilitre (µg/ml), whereby care must be taken whether we are discussing:

- µg ozone per ml ozone/oxygen mixture,
- µg ozone per ml blood, or
- the total quantity of ozone in µg per total quantity of blood, or the total quantity of ozone in µg per treatment.

Ozone dosage covers a range from 500 µg to max. 4000 µg ozone per treatment, using a quantity of blood between 50 and 100 ml. The sometimes recommended blood quantity of 300 ml is to be rejected, as this can present a risk from a haemodynamic viewpoint, especially in elderly or decompensated patients. For blood treatment, concentrations of 80 µg ozone per ml whole blood and above are also to be rejected, on account of the increasing risk of haemolysis (up to 10% at 100 µg ozone per ml whole blood), a decrease in 2,3-diphosphoglycerate (2,3-DPG) and a consequently absent activation of immunocompetent cells. Empirically, in major autohaemotherapy (MAH), concentrations between 10 and 40 µg, in exceptional cases up to 60 µg ozone per ml whole blood, have demonstrably shown themselves to activate cellular metabolism and have immunomodulatory effects as well as a regulatory effect on the intracellular antioxidants.

Indication	O_3 quantity in µg	Treatment frequency	Number of treatments
1. Arterial circulatory disorders			
Cerebral and peripheral, stage II	800 - 1000 µg per 50 ml blood	2 x per week	Series of 10 treatments 2—3 x per year
Stage III and IV	1000 - 1500 µg per 50 ml blood	daily at first, then 2 x per week	
2. Immunoactivation			
Geriatrics	800 - 1500 µg	2 x per week	Series of 10 treatments 2 x per year
Preventive vs. infection	1000 - 1500 µg	2 x per week	Series of 6 treatments 2 x per year
Adjuvant in cancer therapy	500 µg – 1000µg	2 x per week	Series of 10 treatments several times per year or : 2 treatments per month after the 1st treatment series (continuously)
3. Infections			
Hepatitis, A, B, C			several series
Acute	2000 µg in 70 -100 ml blood	daily	as per control
Subsiding	1500 - 2000 µg	2 x per week	as per control
Chronic	1000 -1500 µg	1 - 2 x per week	as per control
Herpes zoster			
Acute stage	2000 µg in 50 - 100 ml blood	daily in the 1st week	1 series of 10 treatments
post acute	1000 -1500 µg in 50 ml of blood	2 x per week	as per control
4. Inflammatory Processes			
Rheumatoide arthritis			
Acute stage	1500 µg in 50 ml blood	daily in the beginning, then 2x per week	10 treatments at least
Chronic stage	1000 µg in 50 ml blood	2x per week, then 2x per month	as per control

Tab. 3. Recommended ozone doses for reinfusion treatment in Major Auto Haemotherapy, MAH)

Rectal Ozone/Oxygen Insufflation

This is one of the oldest forms of application in ozone therapy. Based on animal investigations and a comprehensive proctological study, rectal insufflation with an O_3/O_2 gas mixture is increasingly being used as a systemic therapeutic form, and is already being viewed as an alternative to MAH (it is the method of choice in paediatrics).

Indications

Local

- Ulcerous colitis
- Proctitis, stages I and II
- Anal fistulae and fissures

Systemic

- Indications cited for MAH
- Hepatitis B and C
- For immunomodulation (complementary method in oncology)

Method

A rectal insufflation set consists of:
An ozone supply container with lock valve, dosing bag with non-return valve, connecting tube with luer/luer lock or 50 ml silicone-coated disposable syringe and rectal catheter.

Dosage

- Systemic: 10-25 µg ozone/ml oxygen gas mixture, volume 150-300 ml; for children: 10-20 µg/ml, volume 10-30 ml

- Local: in ulcerous colitis, high O_3/O_2 concentrations (60-80-100 µg/ml) and small volumes (50 ml) are applied; on cessation of haemorrhage, this is reduced to 30-20 µg/ml, followed by systemic efficacy: 10-20 µg/ml, 150-300 ml volume.

Rectal ozone application is simple, low-cost and practically free of adverse reactions when dosages are adhered to exactly.
As an adjuvant therapy in proctitis and proctocolitis, rectal insufflation is scientifically founded and to be recommended. Rectal O_3 insufflation is being increasingly used in paediatrics, sports medicine, geriatrics, and as a complementary method in oncology.

Minor Autohaemotherapy with Ozone

As a non-specific immuno stimulant therapy

Indications

- Acne vulgaris (common acne)
- Allergies
- As an adjuvant in cancer therapy
- Immunoactivation

In Minor Autohemotherapy, under aspetic conditions, 2-5 ml blood is removed intravenously and drawn into a sterile, pyrogen-free 30 ml disposable syringe (containing already the ozone-oxygen mixture), where it is mixed with 10 ml of an O_3/O_2 gas mixture, strongly shaken and slowly reinjected intramuscularly in the ventrogluteal region. Ozone concentration: 10-20 µg/ml.
(caution: never fill a blood containing syringe at the ozone generator!)

Topical Ozone Applications

In the local application of an O_3/O_2 gas mixture externally to the skin or to wounds, already practiced during the First World War, it was the disinfectant and deodorizing effect of ozone that stood in the foreground. It is now known that, with the topical application of O_3/O_2 gas mixtures, from ozonized water or ozone cream (ozonides) and beyond, a wound healing effect is produced which is being made use of to an increasingly successful extent.

Indications

- External ulcers (ulcus cruris, decubitus ulcers)
- Burns, superinfected
- Skin lesions (wounds)
- Local infections (smear infections, herpes simplex, herpes zoster, mycosis)
- Eye injuries and infections.

Application forms

- Ozonized water (acute treatment: e.g. injuries, burns, ulcers, as intraoperative rinsing)
- Pressure-free application in ozone-resistant plastic bags, in the form of transcutaneous O_3 rinsing (e.g. ulcus cruris, immune vasculitis)
- Subatmospheric ozone gas application under an ozone-resistant suction cup (e.g. decubitus)
- O_3 gas application in the low-pressure plastic boot ("Rokitansky boot") (e.g. diabetic gangrene)
- Ozone cream (ozonides) for long-term treatment: e.g. lesions, burns.

Ozonized Water

In topical applications, the use of ozonized water is now gaining in importance . Ozone is present in water in molecular form, i.e. as triatomic oxygen, presenting a physical solution. When using bidistilled water (aqua bidestillata) and a high-quality ozone generator, a maximum saturation of approx. 20 µg ozone per ml of water at room temperature can be obtained. It reacts immediately on skin contact, contrary to ozonides, such as e.g. ozone cream, which have a long-term effect.

Indications

- Local infections
- Ulcus cruris
- Decubitus ulcers
- Mycosis, mycotic infections

- Herpes simplex and herpes zoster (also including subcutaneous ozone injections where required)
- Burns, also superinfected burns
- Intraoperative rinsing
- Eye injuries and infections
- Surgical scars (healing: primary or secondary)
- Oedemas of traumatic or bacterial origin.

Methods and Dosage

For 5-15 minutes, allow an ozone/oxygen gas mixture at an O_3 concentration > 100 (10 min) or 60-80 µg/ml (15 min) to pass in the form of small bubbles through 1 litre aqua bidestillata with a water column of approx. 40 cm. In bidistilled water, the half life of ozone is approx. 10 hrs at room temperature, the concentration remaining approx. 18-24 µg/ml at 20 °C [68 °F]. In the refrigerator, ozonized bidistilled water can be kept for approx. 5 days. Overdosage is not possible, as the dose is limited by the solubility of ozone in water, approx. 24 µg/ml for aqua bidestillata. Ozonized water is basically applied on account of its pain-relieving, disinfectant and antiinflammatory effects, as well as its tissue-activating properties in acute and chronic injuries with and without infection, which are being applied with increasing success. In the foreground, however, the elimination of perifocal oedema is to be found. But also intraoperatively, as in hand surgery , in dental medicine and particularly in oral surgery ozonized water is being used for rinsing. The healing time for primary scars is shortened and irritation-free. In a number of cases, long-term treatment can be continued using peroxidic oils.

Ozone cream (Ozonides and Peroxides)

As reaction products of O_3 and unsaturated fatty acids, ozone peroxides and ozonides also stimulate wound healing, which could be demonstrated for burns and mechanical injuries in a study involving animals.
Peroxidic oils are used for the long-term treatment of injuries, burns and local infections such as skin and nail mycosis, as well as in the follow-up treatment of ulcus cruris and decubitus ulcers.

Topical Treatment as Transcutanous Gasbath (bagging)

The transcutaneous "ozone gas immersion" method is a method of choice in extensive, deep topical infections. Here, after moistening the extremity to be treated or the area over the organ concerned, direct O_3 gas immersion is applied inside a sealed, ozone-resistant plastic bag, or in a slight vacuum using a special, low-pressure "boot" or inside a low-pressure cup.

Indications

- skin lesions, burns, superinfected wounds (surgical scars), diabetic foot, phlegmons (erysipela)
- large-surface, open and deep chronic ulcers, possibly infected, decubitus ulcers.

In transcutaneous ozone gas immersions or low-pressure applications used in the treatment of infected ulcers, the O_3/O_2 mixture is initially applied at higher concentrations (70-100 µg/ml) after moistening of the area to be treated. Its microbicidal and virus-inactivating effect already takes place at lower concentrations (< 40 µg/ml). Once wound healing has actually started, the concentration can again be reduced (< 20 µg/ml), thus making full use of the metabolically stimulant and immunomodulatory effect of ozone as the healing process continues.

Low-pressure ozone treatment is not a monotherapy, as the other forms of wound treatment (biocompatible dressings, wound cleansing, enzymes where required) must continue in use, according to the condition of the wound and in conformity with current rules. The considerable local hyperaemic effect due to the mildly subatmospheric conditions plus the properties of ozone contribute to the healing process.

Intraarticular Ozone Injections

Intraarticular ozone injections in acute and chronic, painful joint conditions represents a complementary treatment method which provides rapid pain relief, decongestion, subsidence of bruises (haematomas), a reduction in temperature and an improvement in motility. It involves knee and shoulder joints presenting chronic pathological symptoms.

Indications

- Symptoms of the rheumatic and degenerative type, diseases and injuries of the joints (arthrosis, arthropathias)
- active gonarthrosis, acute diseases of the shoulder joints involving partially restricted functional movement (shoulder stiffness)
- chronic shoulder joint conditions with calcification and painfully restricted movements in the final stage.

Intraarticular ozone injection is increasingly being applied with success, particularly in orthopaedic practices, where inflammatory and degenerative diseases of the bones and joints as well as posttraumatic conditions (i.e. following sport injuries) and surgery of the large joints are involved, cases in which additional MAH has a supportive and stabilizing function.

Performance

Prior to ozone application, the standard injection points can be infiltrated with a slow-acting local anaesthetic. For intraarticular ozone injections, a volume of approx. 20 ml shoulder and knee, for periarticular and subcutaneous infiltrations a volume of 10 ml is used. In each case, the ozone concentration is 10-15 µg/ml.

Intraarticular injection of an ozone/oxygen gas mixture must be considered as being an invasive intervention in a sterile system (joint), to be carried out under specially strict aseptic precautionary measures (Tab. 4). In addition the ozone unit must be cleaned every day after use as hygiene requires (see manufacturer's instructions), and additionally disinfected by wet wiping with corresponding agents (surface disinfectants) when contamination with blood has occurred. Regular maintenance of the unit must also be counted as hygienic safety. The aseptic steps recommended agree for the most part with those issued by the “German Orthopaedics and Traumatology Association”, the Orthopaedic Physicians' Professional Association, and the

"Guidelines on Intraarticular Injection Procedures" published by the Hospital Hygiene Work Group. These Guidelines continue to be the officially recognized standard for medical experts and lawcourts, and should carefully be adhered to.

For intraarticular injections, special aseptic precautionary measures are necessary to prevent infection! [see e.g. “German Orthopaedics and Traumatology Association” (Deutsche Gesellschaft für Orthopädie und Traumatologie) Guidelines] Caution: To avoid general or local infections and skin lesions at injection site and surrounding area:
▪ Hygienic hand disinfection using an RKI/DGHM listed (or equivalent) alcohol-based detergent. Always allow > 30 secs for it to take effect. In cases of suspected HBV or HCV etc. virus carriers, allow for 5 mins before treating or, even better: use (sterile) disposable surgical gloves! ▪ Alternatively: after surgical hand disinfection, put on sterile surgical gloves, sterile protective clothing, and use sterile cloth covers around the injection site (e.g. when in contact with the patient's skin over the area under treatment) ▪ Disinfection of skin at treatment site using an RKI/DGHM listed (or equivalent) alcohol-based disinfectant: spray liberally over site and gently rub in with a sterile gauze swab. Allow > 1 min to take effect ▪ From the teflon valve of the supply unit, remove the prescribed quantity of medical ozone / oxygen gas using a sterile, silicone-coated 50 ml disposable syringe with a preconnected bacterial filter ▪ Using a long, thin, sterile disposable cannula, e.g. 0.8 x 40 mm (size 2 metric) or 0.6 x 60 mm, inject the ozone/oxygen gas mixture ▪ Immediately cover the injection site with a (sterile) quick-action wound dressing.

Tab. 4. Aseptic procedure for intraarticular ozone injection

Subcutaneous and Intracutaneous Application (O_3/O_2 blistering)

Indications

- Herpes zoster
- Neural therapy
- Tonanalgetic systems

Intradiscal Injections

Intradiscal injections cannot be done except under imaging-system control in the concerned departments of hospitals, see special publications .

List of Publications on demand.

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