Extracorporeal blood oxygenation-ozonation (EBOO)
ISCO3/MET/00/22

Index

Title: ISCO3/MET/00/22 Extracorporeal blood oxygenation-ozonation (EBOO)

1.1. Brief background

Despite the high efficiency of mayor auto hemo therapy (MAHT) procedures, they do not always provide the desired therapeutic effect, particularly in the treatment of infectious diseases for which it is desirable to subject patient's blood, as much as possible, to the treatment by ozone. An alternative method is Extra Corporeal Blood Oxygenation - Ozonation (EBOO). The method combines the process of blood autotransfusion and its ozonation-oxygenation in the external circuit. Such approach theoretically allows to ozonate the entire circulating blood volume in a single procedure.

International Society of Blood Purification recognizes EBOO as a method that can reduce a viral load in patients with chronic hepatitis.[1] A clinical trial has shown that EBOO procedure was more effective in the treatment of peripheral artery disease than prostacyclin.[2] In some studies EBOO has shown clinical effectiveness: necrotizing fasciitis[3], severe peripheral arterial disease, coronary disease, cholesterol embolism, severe dyslipidemia, Madelung disease, and sudden deafness of vascular origin.[4]

There has been performed a number of cardiac surgeries with cardio-pulmonary bypass that have used EBOO during the operation.[5,6] Later on, this technique has been refined by the group of Italian.[7-9] and the Malaysian researchers.[10] Ukrainian scientists have developed a unique modification to the EBOO procedure- rotary-film contactor, made of glass and polypropylene.[11] .

1.2. Purpose

The purpose of this SOP is to describe the extracorporeal blood processing procedures with ozone and oxygen (EBOO).

1.3. Scope

This procedure specifies the blood collecting technique, doses, volume of gas and frequency of ozone application.

1.4. Acronyms, abbreviations and definitions

BV	The volume of blood that has been treated with ozone-oxygen mixture in the contactor of this procedure
CBV	Circulating Blood Volume
EBOO	Extracorporeal Blood Oxygenation and Ozonization
GED	Gas-Exchange Device (or contactor)
MAHT	Major Autohemotherapy
OOM	Ozone Oxygen Mixture
SOP	Standard Operation Procedure
Total dose	Total amount, in micrograms, of ozone given per session, calculated as volume in mL multiplied by concentration in µg/mL

2. Responsibility

Physician
Patients' Clinical records registration (ISCO3/REC/00/02).
Assessment of the indication, contraindications
Request the informed consent (ISCO3/QAU/00/21) and the privacy consent
Applications and monitoring
Prescription of investigations to assess the effectiveness of the treatment (e.g. microbiological or immunological assays)
Reporting any late complications (ISCO3/REC/00/03)
Patient follow-up

Nurses
Accommodate the patients
Preparation of the clinical procedure
Supervision of patients, and vital signs control
Detects and alerts the doctor to anomalies due to possible reactions
Notification of possible complications

The EBOO procedure must be performed by physician who is specially trained in ozone therapy and who is also has been trained in the EBOO procedures. The protocol of the EBOO procedure also recommends to have a specially trained assistant or nurse, especially during the initial and the final stages of the procedure.

Procedure should be done only in centers who have legal approvals to perform standard hemofiltration or dialysis.

3. Procedure

3.1 Indications

- ✓ Severe peripheral artery disease
- ✓ Cardiac ischemia
- ✓ Severe dyslipidemia
- ✓ Necrotizing fasciitis[3]
- ✓ Severe bacterial infections that are resistant to antibiotics
- ✓ Ischemic stroke
- ✓ Chronic heart failure
- ✓ Viral hepatitis type a, b and c
- ✓ Acquired immune deficiency
- ✓ Chronic inflammatory processes
- ✓ Pre-treatment for patients who are planning to undergo antiviral therapy medication

3.2 Contraindications

Absolute contraindication: Favism: Glucose-6-phosphate dehydrogenase deficiency (favism, acute haemolytic anaemia).

In, pregnancy use only in serious diseases for the mother when other approaches are not successful or available.

Relative contraindications / special situations:

- ✓ Uncompensated diabetes
- ✓ Recent Acute myocardial infarction
- ✓ Uncompensated toxic hyperthyroidism - Basedow Graves status
- ✓ Thrombocytopenia less than 50.000 and serious coagulation disorders
- ✓ Severe Cardiovascular instability
- ✓ Acute alcohol intoxication
- ✓ Massive and acute hemorrhage
- ✓ During convulsive states
- ✓ Hemochromatosis
- ✓ Patients receiving treatment with copper or iron.

3.3. Recommended doses intervals

Each procedure of EBOO recommends a treatment of 2.5 L to 7.5 L of blood, which corresponds to 0.5 - 1.5 CBV. BV depends on the condition of the patient, on the balance between optimal speed of outflow / inflow blood for the patient and on the total duration of the procedure.

Experience has shown that the duration of the whole procedure, including the stage of preparation, should not exceed 2 h. When the blood flow velocity will reach 20 mL / min to 50 mL / min (optimum speed - 30-35 mL / min) - 1.2 L to 3.0 L (1.8 L-2.1 L) of blood will pass through the EBOO contactor.

The contactor (patented and described in reference 10), consists of a glass vessel rotating at low speed (rotational speed can be varied from 5 to 35 turns / min, depending on the substitution rate of blood in the contactor). The Ozone oxygen gas mix enters into the contactor at a constant rate of 300 mL / min with ozone concentration set between 0.1 µgN/mL to 0.4 µgN/mL. At a flow of 300 mL/min for 1 h passed through the contactor 18 L of ozone-oxygen mixture. If the ozone concentration of (0.1 - 0.4) µgN/mL the total amount of ozone will be (1.8 - 7.2) mg. When processing large volume of blood is planned, ie procedure last longer than 1 h, use a concentration of ozone (0.1 - 0.3) µgN/mL, and the dose of ozone for 2 h will be (3.6 - 10.8) mg. Duration of treatment for more than 2 h is not recommended, especially if the selected ozone concentration was higher to 0.3 µgN/mL. Blood contacts the walls of the contactor where it get exposed to the oxygen and ozone saturation. On the walls it creates thin layer of film where the saturation takes place. At the maximum rotation speed, the area of blood saturation reaches the surface of 2.5 m^2 / min.

It is not recommended to treat more than 1.5 CBV per week. EBOO is recommended to be carried out between one procedure per week to one procedure per month, subject to the prescribed course of treatment. Each course usually runs for up to 4 treatments (with 1 treatment per week). The optimal frequency of the sessions is about 2 times per year.

During the EBOO procedure, the external (extracorporeal) blood volume should not exceed 200 mL, to prevent any risk of hemodynamic instability, and it is desirable to maintain an extracorporeal blood temperature at 37º C, to avoid patient hypothermia.

3.4 Clinical evaluation

A clinical and/or laboratory evaluation is necessary to establish an accurate diagnosis and to permit comparisons between the patient's status before, during and after the ozone therapy. Attention also should be given to the subjective data from the patient (ex: I feel more energy and less tired).

3.5 Preliminary operations

The patient must be fully informed in advance about the method itself, all the steps of the procedure, the desired effect(s) and also about the possible unwanted side effects. Also a written Consent form should be read, understood and signed by the patient or an authorized patient's representative prior to the EBOO procedure.

The duration of a procedure - a minimum of 1 h, so the patient should be laid on a couch or bed, providing that the bed has an access to it on both sides. The preparatory phase of this is no different to any other standard hemofiltration procedure.

Requirements: intravenous catheters, 20 G size (1 mm diameter) or 22 G (0.8 mm diameter). Heparin solution (5000 IU –in 1 mL).

3.6 Device

The primary goal the EBOO procedure - is to expose a lot of blood to the Ozone treatment. The main difficulty in the practical solution of this problem is the need for highly efficient flow heterophasic contactor (gas-liquid interface), capable to effectively and safely perform with a such reactive gas like ozone.

All components of the contactor should only be manufactured from materials resistant to ozone, e.g., glass and polypropylene. Do not use dialyzers intended for hemodialysis, since they are made of polysulphone, acrylonitrile, methyl methacrylate, polisintane and / or other plastics that are sensitive to ozone. Ozone changes significantly the gas exchange properties of such filters. The exposure of such filters to ozone can lead to the blood contamination from the toxic degradation byproducts.[6-9]

Currently, there are two types of contactors which meet the requirements of safe ozonation-oxygenation of large volumes of blood in the external circuit:

1 - specially developed in Italy the contactor from polypropylene.[8]
2 - the developed in Ukraine rotary-film contactor made of glass and polypropylene.[11,12]

The contactor described in reference 6, contains the polypropylene fibers, hollow inside and covered from outside by phosphorylcholine. Blood contact the fibers on the outside. The Ozone –Oxygen gas enters from the inside of the fibers and moves in the opposite direction. It consists from the 99% oxygen and 1% of ozone. Across the fiber wall with the thickness of 50 microns the gas contacts the blood. The "contact" area estimates 0.22 m^2.

3.7. Main procedure

Catheters are introduced into the cubital vein, apply a tight bandage on the puncture veins. Flushed with heparin solution - 0.5 mL of heparin, 5000 IU in 1 mL (total 5 000 IU). The contactor and lines for blood filled with saline with heparin, 2500 IU / 100 mL (approximately 100-200 mL of solution, i.e. more 2 500 IU - 5 000 IU, but in total a maximum amount of 10 000 IU).

Once the catheters are set, we can start to draw the blood into contactor, and after the Ozone-Oxygen saturation in the contactor the blood returns through another vein. All the time, physician should observe the procedure. For heparin "half-life" (i.e., time on the inactivation of 50%) - 30 min. In one hour, only 25% of the heparin will be active. If you plan to continue the procedure or notice signs of thrombosis in the contactor (such as clogged filter in the blood return line) - it is necessary to introduce an additional 2 000-3 000 IU of heparin.

If, at the end of the procedure, the active heparin level in the blood is more than 5 000 IU, it should be inactivated. Calculate the amount of residual heparin, and enter Protamine Sulfate 1% solution at the amount of 1.5 mg (0.15 mL of a 1% solution) per 100 IU of heparin, but not more than 5 mL 1% - solution at a time. Enter protamine slow. If you enter protamine more than necessary, he will cause a reduction in blood clotting, so be careful when calculating doses. If heparin activity is less than 2 000 IU, it is better not to use protamine.

3.8 Warning

Avoid:

✓ Intravenous injections and transfusions under pressure (which may cause air embolisms).

3.9. Patients Follow-up

Patients may be followed up and re-evaluated from time to time, from the clinical / subjective point of view and/or with laboratory and/or image examinations.

3.10 Contingencies; Corrective Actions

Some patients react very sensitively to the pain caused by the insertion of a needle. They may feel dizzy, may sweat profusely, and even faint. It is very convenient to have an electric table which allows a Trendelenburg position. Emergency bottles of saline, injectable glucose, injectable vitamin C should be at hand. In extreme cases, an oxygen mask might be required. The patient should not have fasted too long before the EBOO, but also should not come immediately after a large and heavy meal. The ingestion of alcoholic beverages should be discouraged for the 24 h after the EBOO.

In case of other side effects follow the instructions of ISCO3/CLI/00/01 "Fist Aids in ozone therapy (Inhalatory exposition and accidental over dose)" and report the side effect using ISCO3/REC/00/03 "The ISCO3 Safety Information and Adverse Event Reporting Program Form".

4. Effect Mechanism

The therapeutic benefits of EBOO will be mainly in the following areas:[3,4,13,14] (clinical trial should be done).

a) Critical, inoperable ischemic limbs (stage III and IV, Leriche-Fontaine) when amputation remains the only option. Medical treatments (iloprost infusion, pentoxyphylline, electrical spinal-cord stimulation, anticoagulants, platelet anti-aggregation, anti-atherosclerotic drugs, etc.) help but are rarely successful.[3]
b) End-stage ischemic myocardiopathies, previously operated on with no success;
c) Acute cerebral ischaemia, to be treated with EBOO as soon as possible to reoxygenate the hypoischaemic (penumbra) and infarctuated areas, thus limiting neuronal death and favoring a more rapid recovery.
d) Chronic HCV hepatitis in patients who are resistant or intolerant to antiviral treatments or because they refuse orthodox therapy;
e) Chronic renal failure, which is always accompanied by immunosuppression and a chronic oxidative stress continuously aggravates the metabolic disorder. In such a case, the oxygenator may be situated parallel to the dialysis filter and used following the dialysis session after a bolus infusion of antioxidants to reconstitute a sufficient antioxidant capacity depleted during dialysis.

In other diseases, such as:

f) Metastatic, chemoresistant cancer and severe primary or secondary (to HIV-protease inhibitors treatment) lypodistrophies, the usefulness of EBOO remains to be considered against the validity and cost-benefit of this approach.

5. References

5.1 SOP References

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6. Change History

SOP no.	Effective Date	Significant Changes	Previous SOP no.
ISCO3/MET/00/23	22/03/2016	Draft.	First version
	15/07/2016	Draft 1 was amended according to suggestion (mainly typographical), referenced was edited. Critical point highlighted in red remain unclear. Document back to the discussion forum, expected to be approved on September 2016	Draft 2
	03/10/2016	Draft 2 was amended according to suggestion. Critical point about dose and the use of anticoagulant, highlighted in red remain unclear. Document back to the discussion forum, expected to be approved on October 2016	Draft 3

7. Document Records

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