PROTOCOL

Inorganic nitrates in pulmonary embolism with hemodynamic instability

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Content

1. Background

Pulmonary embolism (PE) causes an obstruction of the lung circulation. High-Risk PE puts sudden strain to the right side of the heart and, when causing hemodynamic instability, is an acute life threating condition(1). It is the third most common acute cardiovascular syndrome (2), and causes hundreds of thousands of deaths each year in the US and EU (3). The incidence of PE is increasing, mainly due to an aging population(4).

The mechanism of hemodynamic compromise in acute PE is multifactorial (5), involving a combination of mechanical obstruction of blood flow in the pulmonary artery, as well as increased pulmonary vascular resistance (PVR) due to hypoxic vasoconstriction and endogenous production of other vasoactive agents. Further, the high right ventricle (RV) pressure and dilatation diminishes coronary blood flow, exacerbating RV failure leading to decreased stroke volume.

Typically, PE is classified into risk subsets where high-risk is defined as PE and hemodynamic instability and intermediate-high-risk as PE with RV dilatation and elevated troponin levels(3). The fundamental treatment of intermediate- and high-risk PE aims to rapidly remove clots leading to reperfusion, together with supportive care provided as needed(3). The primary cause of death in PE is often RV failure (6). In the literature, a mean pulmonal arterial pressure (mPAP) above 40 mmHg is described as the upper boundary of what a non-adapted RV can handle without failure. However, this boundary originates from small studies in the 1970s (6).

The use of vasodilators to improve hemodynamics by treating pulmonal hypertension (PH) is mechanistically appealing but clinical evidence for its efficacy and safety is scarce (7). In animal models of acute PE, vasodilators decreased PVR and led to improved hemodynamics (8-10). A recent Danish RCT investigated the effect of the vasodilator Sildenafil in patients with intermediate high-risk PE (11). The trial did not show any effect on the primary outcome but demonstrated that right heart catheterization (RHC) and vasodilators seems safe in patients with intermediate high-risk PE. New and larger studies are warranted that describe invasive hemodynamical parameters and vasodilatation in severe pulmonary embolism.

In this study we will perform measurements with RHC at admission in intermediate high-Risk PE-patients in order to describe invasive hemodynamics, and also investigate the hemodynamic response to vasodilatation with inorganic nitrate compared to standard care in the same cohort with a placebo double blinded randomized controlled trial (RCT).

2 Rationale for trial

This study will be the first double blinded RCT to investigate if oral inorganic nitrates are beneficial and safe in intermediate high-risk PE. Also, the current trial will be one of very few studies examining invasive hemodynamics in intermediate high-risk PE.

3 Aims

a) To Investigate baseline invasive hemodynamics parameters among patients with intermediate high-risk PE.

b) To investigate safety, feasibility and physiological effects of vasodilation with inorganic nitrate in patients with intermediate high-risk PE in a double blinded randomized controlled trial (RCT).

4 Hypotheses

a) mPAP in patients with intermediate high-risk PE is elevated at arrival to the ICU.

b) Inorganic nitrate will reduce mPAP with 20% or more after 3 h compared to placebo.

5 Inclusion and exclusion

Inclusion criteria:

- Acute PE with symptoms < 14 days confirmed by computer tomography (CT)

  AND
- RV dilatation on CT or ECHO
- Troponin T > 45 pg/ml

Exclusion criteria:

- Cardiac arrest with cardiopulmonary resuscitation
- Thrombolysis or endovascular thrombectomy
- < 18 years of age
- Pregnancy
- INR > 2,5 or platelet count < 100
- DAPT or OAK
- Inability to give informed consent to the study
- Contraindications for right heart catheterization: mechanical devices, endocarditis, GUCH-patients

- Short expected lifespan< 120 days/withdrawal of care
- Imdur or other medications with nitrates
- Daily usage of mouth wash prescribed by dentist or doctor.

6 Methods

A multi-center, double blinded randomized controlled study conducted at Södersjukhuset and Karolinska Universitetssjukhuset Huddinge.

6.1 Patients

Patients with intermediate high-risk PE who fulfill the inclusion criteria and none of the exclusion criteria are available for eligibility and inclusion in the study after informed written consent.

6.2 Treatment and randomization

After diagnosis, the patient is transported directly from the emergency department to the coronary critical unit (CCU) or the intensive care unit (ICU) or high dependency unit (HDU) and started on standard care treatment. An eligible patient is contacted by the physician in charge, as soon as possible on arrival to the CCU/ICU/HDU, who verbally and in writing give information about the study. If necessary, the physician must give appropriate time to the patient for reflection before giving their consent. Inclusion must be made no later than 3 hours after admission to the CCU/ICU/HDU. The patient can withdraw their consent and participation in the study at any time.

All patients included in the study will receive standard treatment with low-molecular-weight-heparins (LMWH) or heparin-infusion, decided by the treating physician.
All patients included will receive a RHC and invasive hemodynamics will be collected at baseline according to a standard protocol.
After completing invasive hemodynamics at baseline, patients will be randomized 1:1 to intervention (inorganic nitrates) or control (placebo).

Intervention:
Patients randomized to intervention will directly after randomization receive a dose of two shots of beetroot juice 7 cl (KNO_3: 6 mmol each corresponding to 744 mg nitrate) and continue with this daily dose for a total of five days.

Control:

Patients randomized to control will directly after randomization receive two shots of placebo beetroot juice 7 cl and continue with this daily dose for a total of five days.

Dosages and length of intervention equals the NITRATE-CIN protocol(12).

Three hours after intervention or placebo the second round of invasive hemodynamics will be completed to assess the primary outcome. The intervention is blinded to the treating physician, the investigators and the patient. Randomization is performed by a web-based randomization tool.

7 Outcomes

Primary outcome:

- mPAP 3 h after administration of study treatment

Secondary outcomes:

- Hemodynamic physiological parameters (RAP, RVP, dPAP, sPAP, mPAP, PaWP, CO, CI, SVR, PVR, SVO2, AW-diff, RA-saturation) at baseline, 3 h and 24 h
- Difference in troponin 24 h after administration of study treatment compared to baseline
- Concentration of nitrate in blood and saliva at baseline and 3 hours after administration of study treatment

Safety outcomes:

- Mean arterial pressure (MAP) < 55 mmHg (Yes/No) after study treatment
- Use of vasopressors after administration of study treatment (yes/no)
- Bleeding, arrhythmia, infection, pneumothorax as a result of RHC
- Allergic reaction (typ 1) to study treatment
- Death

Feasibility parameters:

- Numbers and proportion of patients with successful baseline invasive hemodynamics with RHC.
- Numbers and proportion of patients with successful invasive hemodynamics at 24 hours.
- Numbers and proportion of patients randomized that completed the study protocol.

Exploratory endpoints:

- ECHO bedside at baseline and at 72 h from baseline.

- Creatinine, Pro-BNP, CRP, ASAT, ALAT, at baseline and then 24 h, 48 h and 72 h from baseline
- Arterial blood gas at baseline and 3 h and 24 h after intervention analyzing oxygen saturation, MetHb, and lactate.
- FiO2 at base-line and 3 h, 24 h and 48 h after intervention.
- Vasopressor (Yes/No).
- Invasive ventilation (Yes/No).
- Non-invasive ventilation (Yes/NO)
- Cardiac arrest (Yes/NO)
- Time to discharge.
- Rescue therapy with thrombolysis or thrombectomy.
- RV/LV ratio at baseline and 72 h.

8 Outcomes measures and assessment

The invasive hemodynamics will consist of:

1. Blood pressure measured with an arterial line in a. radialis or alternatively with a blood pressure cuff minimum 6 times a day, serving as a safety outcome.
2. Right heart catheterization (RHC) using a 7.5 F continuous cardiac output/mixed venous oxygen saturation/end-diastolic volume pulmonary artery (PA) catheter or a Standard Swan-Ganz catheter in v. jugularis and advanced to the PA. CO is measured with thermodilution or the direct Fick method. All measurements are taken with the patient in a supine position. Wedge pressure is measured as the mean value on expiration. All measurements are recorded at the same time points: at base-line, 3 hours, 24 hours. Systemic vascular resistance and pulmonary vascular resistance are calculated manually. The PA catheter introducer is aseptically placed on the right or left side of the neck into the internal jugular vein using ultrasound-guided Seldinger technique. The PA catheter, encased in a sterile sleeve, is advanced with guidance from pressure waveforms and, if necessary, ultrasound. In exceptional cases, fluoroscopy may be used to overcome difficulties in obtaining pressure waveforms or confirming the catheter's position. However, at least one bedside chest x-ray will be performed to ensure optimal placement of the catheter and rule out pneumothorax.

Echocardiography measurements

1. ECHO with GE apparatus: bedside at base-line: inferior vena cava (IVC) diameter and respiratory variation (>50%, 50%, <50%), right ventricular (RV) basal diameter in A4C, left ventricular (LV) diameter in PLAX, RV/LV ratio, tricuspid annular plane systolic excursion (TAPSE), systolic pulmonary artery pressure (sPAP), visual ejection fraction (EF) > 50%, 40-50

%, < 40% and left ventricular outflow tract velocity-time integral (LVOT-VTI). Standardized echocardiogram on day 3: ECHO-4D protocol including right ventricular strain and FAC.

Other data that will be obtained in the study are:

1. Arterial blood gas from the arterial line.
2. Standard blood samples including the blood samples listed above in the outcome section.
3. Anamnestic report including time of symptom onset, previous thromboembolic events, smoking, ongoing cancer, recent surgery, recent immobilization, current medications, diabetes, and previous medical history will be collected from the patient's medical file.
4. Specific treatment in the ICU including invasive- and non-invasive ventilation, vasopressor, oxygen demand, anticoagulants, trombolys, i.v fluids will be collected from CHA (a medical record from the ICU).

The outcome assessor is blinded to the intervention. The invasive hemodynamics will be stored with the possibility to process the pressure curves and perform calculations. The images from the echocardiography and computer tomography will be stored in systems called Syngo and Sectra respectively. Blood samples and electrocardiograms (ECGs) will be collected from the electronic medical records. Vital signs data will be extracted from the ICU/CCU/HDU medical record system (CHA or TakeCare). Patient characteristic, comorbidity and previous medical history will be collected from the medical file in a system called (TakeCare). All the above data will be stored in a database with anonymized personal data.

9 Safety

In the study protocol RCH and inorganic nitrate are the only interventions not usually involved in standard care that could increase the risk for the patient. Inorganic nitrates have been studied in healthy volunteers, in patients with PAH and also in patients with ischemic heart disease and are considered safe(12-14). Inorganic nitrates are vasodilators and could induce systemic hypotension. The patients have an arterial line, which will ensure the clinicians to respond swift to a drop in systemic blood pressure. Systemic blood pressure is a safety endpoint and a drop in MAP below 55 mmHg for more than 15 minutes or the introduction of vasopressors will be considered an adverse event. At this point the physician is allowed to use vasopressors or inotropes for resuscitation and proceed to thrombolysis or thrombectomy if necessary.

Overall RCH is considered safe, with complication rates at 0,3% when using the v. jugularis interna. Supraventricular tachycardia, hematoma and vasovagal reactions are the most common complications. A rare complication is rupture of the pulmonary artery because of overinflating the balloon. In a big study this complication happened in 1 of 7200 patients(15). The risk for this will be

minimized by a secure lock on the balloon cannula and education about pressure curves and never to inflate if resistance in the cannula. In a recent Danish RCT on vasodilatation with Sildenafil in intermediate high-risk PE, RHC was safe with no complications(11). RCH will be performed by a team of physicians with long experience in the procedure, guided by pressure curves and if necessary, by ultrasound as first choice or fluoroscopy as second choice. All team members, including nurses, will be instructed in the protocol and educated in the procedure. If fluoroscopy is used the radiation dose is very low with no significant implication of risk to the patient or staff(16). In such cases the staff will use lead clothing protection.

In the ICU the patient will be closely monitored and receive standard care in combination with invasive hemodynamics via a RHC that could provide important information on hemodynamics and help the guidance of optimal therapy. Overall, this outweighs the potential risk of inorganic nitrate treatment and RHC for the individual patient. This study could clarify if vasodilation with inorganic nitrate improves pulmonary hypertension and hemodynamics in patients with intermediate high-risk PE. If the study outcome is positive, larger clinical trials could investigate the clinical benefit of inorganic nitrates in intermediate high-risk PE and maybe improve clinical outcome for patients in the future.

9.1 Safety in patients eligible for thrombolysis

Patients with high-risk PE can be eligible for thrombolysis immediately at the emergency department, often due to cardiac arrest or obstructive chock. However, some patients will be border-line candidates for thrombolysis and transported to the ICU for a more thorough evaluation before decision on thrombolysis. These patients could be included in the study if they have no indication for thrombolysis at the time of inclusion. If thrombolysis is indicated later on, they will remain in the intervention and treated according to protocol with the exception of wedge pressure. In this group extra caution and attention to bleeding complications is mandatory throughout the intervention period.

10 Feasibility

The clinical work up and treatment until inclusion is considered standard care. The intervention with inorganic nitrates is considered safe(12). Also, invasive hemodynamics with RHC is considered safe(18) and all the protocols, materials, expertise and experience are available at both study sites (Södersjukhuset Vo. Kardiologi and Karolinska Universitetssjukhuset Huddinge). Prior to the start of the study, education in RHC and hemodynamics will be given all medical staff involved in the study.

11 Statistics

The difference in the primary outcome between baseline and the 3-hour measurement will be analyzed using analysis of covariance (ANCOVA), accounting for baseline measure and the assigned treatment. We performed a power calculated assuming a statistical power of 80%, an α-level of 0.05 and a baseline mPAP of 30 mmHg with a standard deviation of 6 mmHg. This would allow us to detect mean reduction of mPAP of 20% (i.e. 6mmHg) after 3 hours with 15 patients in each arm. A 20 % effect size is believed to be reasonable, and has been used in other trials investigation vasodilation in pulmonary hypertension (17). To account for potential dropouts or missing data and increase the statistical power of the study, we have chosen to include 20% more participants, resulting in 18 patients in each group.

12 Time plan

Södersjukhuset and Karolinska Universitetssjukhuset Huddinge together treat approximately 60-80 patients with high-risk or intermediate high-risk PE every year. We aim at an inclusion rate of 15-20 patients/year across both centers. We plan to begin inclusion in the fall of 2025 and finish inclusion in the end of 2027 and publish the results in 2028.

13 Ethics

Ethical approval will be gained through application to the national Ethical review board in Sweden. The Swedish health and medicine authority (Läkemedelsverket) have been contacted and states that Inorganic nitrates in dietary products such as beetroot juice is not a medical treatment and therefore no further investigation or approval is needed. The study will follow Swedish laws regarding personal data (GDPR). All eligible patients will get written information about the study in an appropriate language. The study will follow the ethical principles according to the declaration of Helsinki. The patients can withdraw their consent and participation in the study at any time.

14 Investigators and Steering Committee

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