Balloon pulmonary angioplasty in chronic thromboembolic pulmonary disease without or with mild pulmonary hypertension: BALLOON-TRIAL

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to assess the effects of BPA on quality of life and exercise capacity in a group of symptomatic CTEPD patients without PH with incomplete recovery after three month of rehabilitation.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Pulmonary vascular disorders
Study type	Interventional

Summary

ID

NL-OMON53967

Source
ToetsingOnline

Brief title
BALLOON-TRIAL

Condition

- Pulmonary vascular disorders
- Embolism and thrombosis

Synonym
chronic pulmonary embolism, chronic thrombo-embolic pulmonary disease

Research involving
Human

Sponsors and support

Primary sponsor: longziekten

Source(s) of monetary or material Support: trombosestichting

Intervention

Keyword: Balloon Pulmonary Angioplasty, chronic pulmonary embolism, exercise intolerance, quality of life

Outcome measures

Primary outcome

The primary outcome is the effect of BPA on the improvement of disease specific quality of life (PEmb-Qol) between the study groups, 6 months after randomization.

Secondary outcome

secondary outcomes include physical performance and endurance measured by the cardiopulmonary exercise test (CPET) and constant Work Rate cycle Test (CWRT), NYHA class and modified BORG scales before and after cardiopulmonary exercise tests at baseline 6 and 12 months following randomization.
Furthermore PROMS for functional status (post VTE functional scale), anxiety and depression (hospital anxiety and depression scale (HADS), work productivity (Work Productivity and Activity Impairment) and generic QoL (EQ-5D-5L), at baseline and after 6,12 and 24 months following randomization. Additionally, incidence of serious advers events will be evaluated.

Study description

Background summary

Up to 50% of acute pulmonary embolism (PE) patients report persistent dyspnea and/or functional limitations despite anticoagulation therapy (1, 2).
Persistent dyspnea and functional limitations may relate to incomplete thrombus

resolution, which cause perfusion defects and by that impairing gas exchange and reducing ventilatory efficiency (6-8). These long-term complications of PE have a major impact on quality of life and has been associated with higher risks of depressive disorders, unemployment, social isolation and excess health care costs (2).

Incomplete thrombus resolution occurs in approximately 30-50% after 3-6 months of anticoagulant treatment (3,4), while chronic thromboembolic pulmonary hypertension (CTEPH), the most serious long-term complication of acute PE, develops in only 2-4% of PE survivors (5). In the absence of PH at rest, this condition is referred to as chronic thromboembolic pulmonary disease (CTEPD) without PH at rest (6-8). Recently, the hemodynamic definition of CTEPH has been updated and expanded (9). The cut-off values for the mean pulmonary artery pressure (mPAP) is lowered from >25 to 20mmHg and for the pulmonary vascular resistance (PVR)form > 3 to > 2.0 Woods units (WU). However although these new cut-off values might better reflect de limits of normal ranges, the new cut-off ranges do not yet translate into new therapeutic recommendations since the efficacy of therapy on patients with a mPAP 21-24mmHg or PVR 2-3 WU are still unknown.

Therapeutic options that are well investigated in patients with the former definition of CTEPH are either surgical removal of the chronic thrombi (pulmonary endarterectomy [PEA]), balloon pulmonary angioplasty (BPA) or PH specific medication (6,9). For the patients with a mPAP < 25,,Hg and PVR < 3, and thus for the majority of patients with functional limitations following acute PE, there is no established therapy yet. Neither is the exact incidence and prevalence and impact on the long-term of CTEPD without PH well known as follow-up studies in which acute PE patients were subjected to repeated imaging tests plus quality of life questionnaires and functional tests are unavailable. However, as with CTEPH with mPAP > 25mmHg and PVR > 3WU (6,9), case series suggest that both BPA and PEA has beneficial effects on hemodynamic and gas exchange parameters in CTEPD patients with mPAP < 25mmHg (10-12). However, PEA is quite invasive and carries a substantial peri-procedural risk (13). Since CTEPD with mPAP < 25mmHg and PVR < 3WU have a better prognosis compared to those with mPAP > 25mmHg and PVR > 3WU, a less invasive procedure would be preferred.

Regarding BPA, two recent, small retrospective studies have suggested BPA is a safe and effective alternative treatment in CTEPD with mPAP < 25mmHg and PVR < 3WU (11,12). Wiedenroth and colleagues (11) performed 35 BPA interventions in 10 consecutive CTEPD patients without PH according the former definition, with significant improvement of WHO functional class, 6-minute walk distance (6MWD) and Borg score. These benefits came at the price of one mild parenchymal bleeding, resulting in hemoptysis. Secondly, Inami et al (12) reported on 15 CTEPD patients without PH, according the former definition, who safely underwent BPA, improvement of exercise tolerance. The median number of BPA sessions was 2 (IQR 1-3), and the median number of vessels treated per patient was 9 (IQR 5-15), which is a lower number of sessions compared to what is routine in CTEPH. No occurrences of reperfusion or pulmonary injuries across the sessions were detected after six months of follow-up. Based on these

results, BPA is regarded as a potentially effective treatment of CTEPD without PH.
We aim to evaluate the effect of BPA in CTEPD patients without PH or with mild PH (mPAP < 25mmHg and PVR < 3WU) on patients reported symptoms, including quality of life, and pulmonary vascular responses to exercise. Because the recovery of exercise intolerance after acute PE may also occur spontaneously (whether or not from further resolution of perfusion defects) and definitely improves after pulmonary rehabilitation, we designed a randomized controlled, cross-over trial to assess the benefit from BPA after at least three months of anticoagulation and three months of pulmonary rehabilitation.

Study objective

to assess the effects of BPA on quality of life and exercise capacity in a group of symptomatic CTEPD patients without PH with incomplete recovery after three month of rehabilitation.

Study design

Mono-center, randomized controlled, open label clinical trial, with an cross-over part and a 6, 12 and 24 month follow-up

Intervention

All patients are subjected to balloon pulmonary angioplasty (BPA); patients who will be first randomized to the BPA arm will undergo BPA sessions the first six months and followed by six to 12 months with no intervention and vice versa: patients who will be randomized to the expectative treatment arm first, will be followed the first six months and undergo BPA six to 12 months following the randomization

Study burden and risks

All patients will be subjected to BPA. Patients are admitted for one day for each BPA session. The study intervention will therefore ask a considerable effort from the patient. In two case series of BPA, including in total 25 CTEPD patients without PH with a median of 2-4 BPA sessions, was one mild bleeding reported (1,2). No other adverse events were reported. Overall, the risk of (serious) adverse events in this study is considered as low, based on an unlikely risk of moderate impact due to one of the exercise tests, and an moderate risk on low or moderate risk of the due to the BPA. Patients randomised to the control arm will be asked not to engage in further rehabilitation and to resume their usual physical activity.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Diagnosis of CTEPD without or with only mild PH (mPAP < 25mmHg and PVR < 3WU), confirmed by a multidisciplinary team of CTEPD/CTEPH experts, based on:
-acute PE that was objectively diagnosed at least 3 months prior to inclusion and adequately treated
-persistent functional limitations: (New York Heart Association (NYHA) class >=2)
-persistent radiological perfusion defects, on any adequate perfusion imaging method: >= 3 segmental perfusion defects
-CPET result with:
a) at least 2 of the following criteria:
• peak VO2 < 80%;
• peak O2 pulse < 80% of predicted;

• V*E/V*CO2 @ nadir > 34;
• Vd/Vt increasing until peak exercise or peak Vd/Vt > 0;4;
• gradual drop of SpO2 of >= 3%;
b) these exercise findings cannot be explained otherwise
2. patients completed a pulmonary rehabilitation program of at least 8 weeks no longer than 2 months before randomization. Depending on the local protocol, sessions could be daily or a few times a week
3. qualifying symptom limited CPET and CWRT were performed after the pulmonary rehabilitation program
4. age 18-80 years
5. Clinical Frailty Scale (CFS) score < 5 (CFS is a 9-point scale that summarizes the overall level of fitness or frailty of an older adult)
6. written informed consent
7. prior treatment or restart with a therapeutic dose of anticoagulation treatment before randomization

Exclusion criteria

1. history of BPA or PEA
2. residual thrombi that are not eligible for BPA, as concluded by the (intervention) radiologists,
3. major acute or chronic cardiopulmonary comorbidities with an expected impact on survival, exercise capacity and/or gas exchange, e.g. significant coronary heart disease, diastolic/systolic heart failure, pulmonary hypertension (mPAP > 25 mmHg), severe chronic obstructive pulmonary disease (COPD) GOLD class >=3, interstitial lung disease (ILD), disabling neuromuscular disease, malignancy
4. inability to undergo exercise tests
5. contrast allergy
6. creatinine clearance < 30ml/min
7. pregnancy or breastfeeding

Study design

Design

Study type:	Interventional
Intervention model:	Crossover
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-09-2023
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO

Date:	15-06-2023
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83240.018.23