Improving treatment of right ventricular failure in pulmonary hypertension patients.

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To explore efficacy and safety of terlipressin in pre-capillary PH patients with RV failure requiring hospitalization.

Ethical review	Approved WMO
Status	Pending
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON46099

Source
ToetsingOnline

Brief title
Improving treatment of RVF in PH patients.

Condition

- Heart failures
- Pulmonary vascular disorders

Synonym
High pulmonary blood pressure, Pulmonary hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: VICI beurs A Vonk Noordegraaf

Intervention

Keyword: Heart failure, Pulmonary hypertension, Terlipressine

Outcome measures

Primary outcome

The aim of this study is: *To explore efficacy and safety of terlipressin as add on therapy to loop diuretics in patients with pre-capillary pulmonary hypertension who are hospitalized for right ventricular failure.* Change in creatinine after 48 hours, is considered as a primary safety endpoint. Endpoint assessment will be after 48 hours and when, in opinion of the clinician an optimal volume status of the patient is reached. Primary efficacy endpoint will be weight loss over the first 48 hours after start of drug administration. This study is considered positive when: The weight loss after 48h is higher in the terlipressin treated patients and change in creatinine is smaller or not significantly increased compared to patients who are treated with loop diuretics alone.

Secondary outcome

Other study parameters and endpoints are:

• Fluid balance (= Fluid intake - urine output) after 48h

• Kidneyfunction after 48h

• Urine output after 48h

• Final dose of loop diuretics at 48h

• Time interval from treatment start to accomplishing an optimal volume status/ time to dismissal

• Change in creatinine at t = 48h, t = 72h and at dismissal

• N-terminal brain-type natriuretic peptide (NT-proBNP) levels

• Total weight loss at t= 72h and dismissal

• Total urine output at dismissal

• Need for additional treatment (in both treatment arms)

Study description

Background summary

Pulmonary hypertension (PH) is a severe disease defined by an elevated mean pulmonary artery pressure (>= 25 mmHg) and pulmonary vascular resistance (>3 Woods units) caused by narrowing of the pulmonary arteries. The increasing pulmonary vascular resistance ultimately leads to right ventricular (RV) failure and death (1).

Although treatment strategies for patients with pulmonary arterial hypertension (PAH) are optimized in the last decades, this has not led to a normalization of PVR. As such, almost all patients continue to develop RV failure. Patients with severe RV failure require hospital admissions for intra venous (IV) loop diuretics in order to reduce fluid overload. However optimal compensation with loop diuretics is rather challenging since patients develop diuretic resistance and deterioration of kidney function. A possible mechanisms of diuretic resistance are both forward failure and renal venous congestion causing an increased renal interstitial pressure, resulting in a hypoxic state and increased hydrostatic pressure in the Bowman*s capsule causing a decrease in glomerular filtration rate (GFR) (2,3).

Despite the considerable burden on patients and survival, consensus on optimal treatment on RV failure in PH patients is currently lacking. PH guidelines recommend the use of diuretics to optimize fluid balance. Vasopressors may be added to preserve systemic blood pressure. To increase cardiac output, use of inotropes (dobutamine) is recommended (1). However these recommendations were based on small studies, mainly including patients with acute RV failure. This is hardly translatable to the PAH population in which patients develop RV failure over years. Optimizing treatment strategies for RV failure in these patients is of utmost importance, to improve bridging strategies to pulmonary transplantation and increase quality of life.

Terlipressin is an arginine vasopressin analogue with a high sensitivity for the vasopressin 1 (V1)-receptor (4,5). Activation of the V1-recptor in the vascular wall initiates vasoconstriction in the peripheral vascular bed. In

rats with hypoxia induced pulmonary vasoconstriction however, arginine vasopressin is known to decrease pulmonary vascular resistance (PVR) and mean pulmonary artery pressure (MPAP) (6). Vasopressin analogues are successfully used in patients with end stage liver failure who develop hepatorenalsyndrome. In these fluid overloaded patients, administration of vasopressors increased systemic vascular resistance, diuresis and GFR (7). In the VU University Medical center terlipressin is added to IV loop diuretics in fluid overloaded PH patients with an insufficient response to diuretics alone. Figure 1 illustrates an end-stage IPAH patient who received terlipressin 1mg/day during admission for fluid overload. In this patient weight loss increased and fluidbalance became more negative after switch from furosemide to terlipressin.

Positive results of vasopressors in RV failing PAH patients were not solely seen in our hospital. Price et al. showed in two young women that vasopressin is eligible as treatment of severe hypotension due to IPAH induced RV failure after delivery by Caesarean section. In one patient Metaraminol, norepinephrine and dobutamine failed in order to increase systemic blood pressure, but after a bolus of vasopressin systemic bloodpressure rapidly restored (8).

With these favorable effects of vasopressors in mind, we hypothesize that in pre-capillary PH patients with severe RV failure, without an adequate response on oral diuretics addition of the vasopressor terlipressin to diuretic therapy will increase systemic blood pressure and renal blood flow by its systemic vasoconstrictive properties. This will result in a reduction of required loop diuretic dose for initiating a negative fluid balance, shorter admission period and a better preservation of kidney function.
Since the incidence of decompensation in pre-capillary PH patients admitted the hospital is low, we will conduct an mono center randomized clinical trial. In this trial we will test the safety and efficacy of addition of terlipressin to a standardized loop diuretic regimen.
This study will be the first clinical trial in RV failure due to end-stage pre-capillary pulmonary hypertension.

Study objective

To explore efficacy and safety of terlipressin in pre-capillary PH patients with RV failure requiring hospitalization.

Study design

The study design is a prospective open label randomized clinical trial.
We will prospectively include 20 IPAH or CTEPH patients, of whom 10 patients will be randomized to loop diuretics and terlipressin, and 10 patients to loop diuretics alone.

Intervention

In this study we will investigate the effect of a low dose of the vasopressin analogue terlipressin combined with loop diuretics vs. loop diuretics alone. Patients who are randomized to the terlipressin arm will be on a dose of 1 mg/day. Terlipressin and the loop diuretics will be administered intravenously.

Study burden and risks

PAH is characterized by progressive pulmonary vascular remodeling and the associated increased RV afterload eventually leads to right heart failure and premature death. Even with maximal treatment, prognosis remains poor: 5 year survival is about 50%.
In end-stage RV failure patients need hospital admissions in order to reduce fluid overload.
Evidence on optimal treatment of these patients is lacking. We therefore believe that this study is of utmost importance. Earlier case reports and our in hospital experience have not shown any adverse effects of treatment vasopressors.

Potential risks of terlipressin are coronary vasoconstriction, hyponatremia and cutaneous ischemia. Benefits of terlipressin are reduction of forward failure by increasing SVR and thus MAP, resulting in an improved kidney perfusion, GFR and diuresis. Patient will require lower doses of loop diuretics, decreasing risks on potential side effects of this drug. Moreover by ameliorating diuresis target weight will be reached earlier resulting in a shorter hospital admission period.
Risk of administration of high dose diuretics is tinnitus or hearing loss. Moreover patients are at risk of kidney function deterioration (increase in creatinine) and electrolyte disturbances, mainly hypokalaemia. Therefore kidney function and electrolytes (sodium, potassium, magnesium, and chloride) will be monitored intensively by blood samples (one sample daily). On the other hand optimizing volume status will give relief of symptoms, decrease preload and finally improve kidney function by decreasing renal congestion.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
• Patients should be diagnosed with pre-capillary pulmonary hypertension either PAH or CTEPH, have clinical signs of decompensated right heart failure, and needing hospital - or ICU admission for IV diuretics.
• PAH (group 1 and 1*) or CTEPH (group 2), diagnosed according ESC/ERS guidelines;
o Mean Pulmonary Artery Pressure (mPAP) >= 25 mmHg
o Pulmonary Arterial Wedge Pressure (PCWP) <15 mmHg
o Other possible causes of PH are excluded
• 18-70 years old
• Increased body weight despite increased dose diuretics in past month
• Clinical signs of decompensation: ankle edema and/or ascites
• eGFR; 30 ml/min/1.73m2
• Sinusrhythm

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
• Pulmonary hypertension due to connective tissue disease, and PH due to left heart disease (group 2).
• Hypoxia defined as SaO2 <=80% and/or <= 90% with oxygen suppletion.
• Pregnancy, lactation

• Anuria (urine production <50 ml/day)
• Known intolerance of loop diuretics or terlipressin
• Recent diagnosis (<1 month ago) of acute pulmonary embolism
• Underlying infectious disorder/ bacteremia
• Known history of occlusive arterial disease (e.g. coronary artery disease) and/or peripheral artery disease, exception: pulmonary embolism
• Type 1 and type 2 diabetes mellitus
• Chronic use of NSAIDs
• Pre-existing renal failure from other causes than forward failure (eg diabetes)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-06-2017
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Terlipressin
Generic name:	Terlipressin acetate
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	02-02-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-03-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-06-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-07-2017
Application type:	Amendment
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
EudraCT	EUCTR2016-001199-31-NL
CCMO	NL57231.029.16