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Nebulized morphine for breathlessness in chronic obstructive pulmonary disease

Submission date 07/03/2017	**Recruitment status** No longer recruiting	[_] Prospectively registered [_] Protocol
Registration date 23/03/2017	**Overall study status** Completed	[_] Statistical analysis plan [X] Results
Last Edited 12/07/2018	**Condition category** Respiratory	[_] Individual participant data

Plain English summary of protocol

Background and study aims
Chronic obstructive pulmonary disease (COPD) is the name given to a collection of diseases which affect the lungs. It is characterised by breathlessness, cough and excess mucus production and is often caused by smoking. Almost all patients with COPD experience dyspnea (difficulty breathing) in their last year of life. Opiod medications (pain relievers such as morphine) are usually offered for end of life care at this stage of the disease. Some small-scale studies support the use of nebulisers (machines which turn drugs into a mist so they can be inhaled into the lungs) to deliver morphine as an alternative treatment for dyspnea. Reports show that delivering morphine in this way can cause less side effects, such as constipation or dizziness. Unfortunately, the effectiveness of nebulized morphine has not been confirmed in larger studies. Recent studies have shown that a large amount of opioid receptors (proteins that bind to opioids and send signals to the brain) are found in the lining of the large airways (windpipe and bronchi - tubes into the lungs). The aim of this study is to compare the effectiveness of nebulized morphine and nebulized saline (salt water), both delivered by the same inhalation system calibrated to target large airways, in treating dyspnea in severe COPD.

Who can participate?
Patients over 50 years old who have severe COPD with dyspnea.

What does the study involve?
During an eight-day stay in hospital, patients receive four days of treatment with nebulized morphine and four days of treatment with nebulized saline in a random order using a special inhalation system designed to target the large airways (wind pipe and bronchi - tubes into the lungs). The intensity of breathlessness is rated on a continuous, 100 mm scale by patients. In addition, the patient's exercise tolerance is measured by a number reading test, which involves asking patients to read numbers aloud for 60 seconds as quickly and clearly as possible, and lung function is measured using specialised equipment.

What are the possible benefits and risks of participating?
Participants may benefit from an improvement to their breathlessness symptoms. There is a

small risk of side effects from the nebulized morphine, such as cough, bitter taste or a pricking sensation in the throat. In rare cases patients may develop tightening of the airways or an allergic reaction.

Where is the study run from?
University Clinical Centre in Gdansk (Poland)

When is the study starting and how long is it expected to run for?
May 2012 to December 2016

Who is funding the study?
Medical University of Gdańsk (Poland)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
ST-553

Study information

Scientific Title
Dosimetrically administered nebulized morphine for breathlessness in very severe chronic obstructive pulmonary disease

Study objectives
2% morphine hydrochloride water solution, nebulized by dosimetric nebulizer calibrated to target large airways, is superior to 0.9% NaCl delivered by the same equipment in treating severe dyspnea in chronic obstructive pulmonary disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Independent Bioethics Committee for Research of Medical University of Gdansk, 25/06/2012, ref: NKBBN/269/2012

Study design
Single-centre randomized double-blind controlled, cross-over trial

Primary study design
Interventional

Secondary study design
Randomised cross over trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Breathlessness in very severe chronic obstructive pulmonary disease

Interventions
Patients are randomly assigned to two treatment sequences using online software for simple randomization (Research Randomizer ver. 3.0).

Each sequence lasts for eight days and consists of two periods, each lasting four days. There is no wash-out between periods. During each period different drug is nebulized: 2% morphine hydrochloride water solution or 0.9% NaCl. Both substances are delivered once daily, in a titrated manner, with the same dosimetric nebulizer until the clinically significant response (i.e. ≥20mm drop in VAS) is reached or substantial side effects occur. MF doses for 4 consecutive days are: 1, 2, 3 and 5 mg.

Intervention Type

Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Morphine hydrochloride

Primary outcome measure
Intensity of breathlessness, measured by visual analogue scale (VAS) 15-30 minutes before the nebulisation, immediately after the nebulisation and 15 minutes, 30 minutes, 1, 2, 3 and 4 hours after the nebulization.

Secondary outcome measures
1. Most effective dose of morphine is noted when ≥20 mm drop in VAS is detected
2. Exercise tolerance is measured using the Wilcock's test 15-30 minutes before and 2 hours after nebulization
3. Safety is assessed by measuring heart rate, respiratory rate and peripheral capillary oxygen saturation at the same time points as VAS, and spirometry and peak expiratory flow (PEF) one hour before and one hour after nebulisation

Overall study start date
01/05/2012

Completion date
20/12/2016

Eligibility

Key inclusion criteria
1. Age above 50 years
2. COPD group D, according to 2013 Global Initiative For Chronic Obstructive Lung Disease (GOLD) guidelines
3. Stage IV airflow limitation i.e. FEV1% < 30%, according to 2011 GOLD classification
4. Breathlessness rated 3 or 4 in the modified Medical Research Council scale (mMRC) breathlessness scale
5. Current non-smoker
6. Written informed consent

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
10

Key exclusion criteria
1. Other coexisting severe chronic lung diseases, such as lung cancer
2. Breathlessness caused by other than COPD chronic diseases, such as heart failure or renal failure
3. Inability to give informed consent
4. previous history of respiratory depression after opioid administration or allergic reactions to opioids
5. Ongoing opioid treatment for any indication
6. COPD exacerbation within the last month

Date of first enrolment
04/03/2014

Date of final enrolment
01/03/2016

Locations

Countries of recruitment
Poland

Study participating centre
University Clinical Centre
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Sponsor type
University/education

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ROR
https://ror.org/019sbgd69

Funder(s)

Funder type
University/education

Funder Name
Gdański Uniwersytet Medyczny

Alternative Name(s)
Medical University of Gdańsk, MUG

Funding Body Type
Government organisation

Funding Body Subtype
Local government

Location
Poland

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer reviewed journal.

Intention to publish date
20/12/2017

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are/will be available upon request from Piotr Janowiak (33033@gumed.edu.pl)

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	11/12/2017		Yes	No