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Morphine for the relief of breathlessness in chronic heart failure (CHF)

Submission date 30/03/2014	**Recruitment status** Stopped	[X] Prospectively registered [_] Protocol
Registration date 19/05/2014	**Overall study status** Stopped	[_] Statistical analysis plan [X] Results
Last Edited 02/09/2019	**Condition category** Circulatory System	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims

Breathlessness is distressing for people with heart failure, and, as the condition worsens, may persist despite the best treatment. Low-dose morphine safely improves breathlessness in other conditions such as cancer and chronic obstructive pulmonary disease (COPD), but we do not know if it helps in heart failure as the two existing studies (of morphine use for 4 days) found different results. There is, however, observed breathing benefit in people with heart failure who have taken morphine for 3 months, but we cannot be confident about this finding as it may have occurred due to chance. Our main aim is to find out whether low-dose morphine therapy taken daily for at least one month is better than a 'dummy' medicine (placebo) for the relief of breathlessness in people with chronic heart failure who are still breathless despite being on the best treatment for their heart condition. We also aim to see whether morphine helps any distress due to breathlessness, enables coping with breathlessness, increases exercise and activity, quality of sleep, quality of life, use of health care services and the severity of the heart failure itself. By comparing morphine with the placebo medicine over 3 months, we aim to find out the unwanted effects due to the morphine itself especially on daytime drowsiness, nausea, constipation and confusion.

Who can participate?

Men and women with heart failure and persistent symptoms despite standard heart failure care.

What does the study involve?

Participants will be randomly allocated (by chance) to receive either low-dose morphine as a capsule taken twice a day or an identical placebo capsule. As constipation is a common side-effect of morphine, all participants taking active morphine will have laxative capsules, and all those taking placebo morphine will have identical 'dummy laxative' capsules. Other than this, all participants will receive the same care and follow up. Benefit from morphine will be calculated at 1 month, but the whole study per participant will last for 3 months so we can gain the best understanding of unwanted effects and any further improvement over that time. Participants will be required to attend the research clinic two times over 3 months. Other assessments can be done by phone or the research nurse can visit at home. Participants will complete the study questionnaires and measures when needed (the research nurse will help) and continue with any treatment the usual medical team advises. The study will measure quality of life, severity of

breathlessness and other symptoms (pain, sleepiness, cognition) using questionnaires. The level of exercise that participants are able to do comfortably will be measured in the clinic with a 6-minute walk test. Activity will also be measured using an activity monitor (like a small matchbox) on the thigh under the clothes, attached with double-sided sticky tape. It can be taken off and repositioned if needed. This measures the number of steps taken and the time spent sitting or lying down. It will be worn for 7 days before the study starts and again during the last 7 days of the first month.

What are the possible benefits and risks of participating?
Although this study may not directly benefit participants, it may improve future treatment of breathlessness. Morphine has been used in medical practice for many years. We therefore know what side-effects might occur. Most patients cope very well with the low doses of morphine that we intend to use. We will check regularly about the known side effects that people can get. These include nausea or feeling sick, constipation or sleepiness. In some people concentration may be affected until they get used to the steady dose after a few days. Therefore participants will be advised not to drive during the first week of taking the medicine. After this time they should carefully consider whether concentration is affected before driving - if in doubt, they should not drive. If side effects persist which may affect driving, participants would need to inform the DVLA. As with any other change in medication, participants should inform their motor insurance company to ensure cover is valid. Although people may worry about becoming addicted to morphine, we rarely see this in people who take it for health reasons. However, if the body has become accustomed to morphine over time, then it may take a few days to readjust when morphine is stopped. This is not expected to be an issue with this study but all participants will receive a phone call in the few days after the end of the study to check all is well.

Where is the study run from?
The study is run from the Castle Hill Hospital in Hull, UK as the lead centre. About 12 centres in England and Scotland will be involved with each centre recruiting 1-2 participants per month.

When is the study starting and how long is it expected to run for?
The study started recruitment in September 2015. Recruitment will be open for up to two years.

Who is funding the study?
The British Heart Foundation (UK)

Who is the main contact?
Professor Miriam Johnson
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Contact information

Type(s)
Scientific

Contact name
Prof Miriam Johnson

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HYMS
Hertford Building
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Hull
United Kingdom
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Additional identifiers

Clinical Trials Information System (CTIS)
2014-000155-81

Protocol serial number
1.0

Study information

Scientific Title
A parallel group, double-blind, randomised placebo-controlled trial comparing the efficacy and cost-effectiveness of 20mg daily oral modified release morphine (MRM) versus placebo on the intensity of dyspnoea in patients with stable severely symptomatic chronic heart failure (CHF)

Acronym
BreatheMOR-HF

Study objectives
The null hypothesis is that there is no difference in the relief of chronic refractory dyspnoea in people with CHF provided by morphine or placebo.

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee North West - Liverpool Central, 16/06/2014, REC ref: 14/NW/0277

Primary study design
Interventional

Study design
Three-month parallel randomised double-blind placebo-controlled trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Heart failure, including failure due to left ventricular dysfunction and failure with preserved ejection fraction

Interventions
Randomised patients will receive either modified release morphine 10 mg capsules twice daily with docusate laxative 100mg capsules twice daily (intervention arm 1) or placebo morphine

capsules twice daily and placebo docusate laxative capsules twice daily (intervention arm 2). To maintain blinding active drug and placebo capsules and their packaging will look the same. The morphine preparation is MST Continus, encapsulated for blinding purposes.

Each participant will take the study medication for three months.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Modified release morphine (MRM)

Primary outcome(s)
Patient-rated average intensity of breathlessness in the past 24 hours using a 0 - 10 numerical rating scale (NRS), where 0 = no breathlessness and 10 = worst imaginable breathlessness, at 4 weeks.

Key secondary outcome(s)
1. Further assessment of breathlessness using 0 - 10 NRS (average/past 24 hours; distress and unpleasantness) and global impression of change (GIC);
2. Assessment of related symptoms using 0-10 NRS (pain) and quality of sleep (Epworth Sleepiness Scale); sleepiness using the Karolinska Sleepiness Scale (KSS)
3. Assessment of functional status (6 minute walk; activPAL™ monitor); and cognitive function (Montreal Cognitive Assessment [MoCA])
4. Quality of life (the Kansas City Cardiomyopathy Questionnaire - short form);
5. Health economic assessment (EQ5D; EQVAS; service utilisation);
6. Toxicity
7. NT-proBNP
8. Dose of diuretic(s) taken by participants
9. Dose of 'as required' immediate release opioid given for breathlessness taken by participants

Completion date
31/03/2017

Reason abandoned (if study stopped)
Participant recruitment issue

Eligibility

Key inclusion criteria
Current exclusion criteria as of 06/07/2015:
1. Patients with New York Heart Association (NYHA) class III or IV symptoms due to heart failure as evidenced by:
1.1. Echo: left ventricular systolic dysfunction (LVSD) <40% ejection fraction (EF), or at least "moderate" on inspection, OR
1.2. Echo showing left ventricular ejection fraction (LVEF) > 40% plus left ventricular hypertrophy, left atrial dilation or abnormal diastolic function

2. N-terminal portion of B-type natriuretic peptides (NT-proBNP) ≥1000 pg/mL OR BNP ≥250 pg /mL within last 3 months
3. Optimal medical treatment of heart failure which has not changed in the previous 2 weeks
4. Adequate renal clearance within previous 2 weeks. glomerular filtration rate (GFR) ≥30ml/min
5. Grade 2 or more on the modified MRC dyspnoea scale
6. Aged 18 years or over

Optimal medical management
This will be assessed by the clinician responsible for the usual care of the patient and reviewed by the study doctor at the recruiting centre prior to study entry. Sub-optimal treatment will be addressed before study entry. Treatment (including dose of diuretic) must be stable for the two weeks prior to randomisation. Optimal treatment for patients with left ventricular dysfunction is defined as:

1. Reached target dose (or be on maximally tolerated dose, or be intolerant) of an inhibitor of the renin-angiotensin system shown to improve prognosis
AND
2. Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis
AND
3. Reached target dose (or be on maximally tolerated dose, or be intolerant) of an aldosterone antagonist
Optimal treatment for patients with normal left ventricular function will be as assessed by their usual clinician.

Previous exclusion criteria:
1. Patients with New York Heart Association (NYHA) class III or IV symptoms due to heart failure as evidenced by:
1.1. Echo: left ventricular systolic dysfunction (LVSD) <40% ejection fraction (EF), or at least "moderate" on inspection within last 3 months, OR
1.2. Echo showing left ventricular ejection fraction (LVEF) > 40% plus left ventricular hypertrophy, left atrial dilation or abnormal diastolic function within last 3 months
2. N-terminal portion of B-type natriuretic peptides (NT-proBNP) ≥1000 pg/mL OR BNP ≥250 pg /mL within last 3 months
3. Optimal medical treatment of heart failure which has not changed in the previous 2 weeks
4. Adequate renal clearance within previous 2 weeks. glomerular filtration rate (GFR) ≥30ml/min
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AND
2. Reached target dose (or be on maximally tolerated dose, or be intolerant) of a beta adrenoceptor antagonist shown to improve prognosis

AND
3. Reached target dose (or be on maximally tolerated dose, or be intolerant) of an aldosterone antagonist

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment
45

Key exclusion criteria
Patients who:
1. Are unable to provide informed consent
2. Are unable to complete baseline study questionnaires even with the assistance of the study nurse
3. Have co-existing malignant disease only if this would affect the study in the investigators opinion
4. Have used morphine-based medications regularly (that is, most days) within the last month above the study dose.
5. Have known true morphine allergies as assessed by a clinician.
6. Have known central hypoventilation syndrome
7. Have been involved in another medicinal trial (CTIMP) within the past four weeks
8. Are pregnant or lactating

Date of first enrolment
01/09/2015

Date of final enrolment
31/03/2017

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
HYMS
Hull
United Kingdom
HU6 7RX

Sponsor information

Organisation
Hull and East Yorkshire Hospitals NHS Trust (UK)

ROR
https://ror.org/01b11x021

Funder(s)

Funder type
Charity

Funder Name
British Heart Foundation (UK) - Clinical Study CS/13/2/30584

Alternative Name(s)
The British Heart Foundation, the_bhf, BHF

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/12/2019	02/09/2019	Yes	No
HRA research summary			28/06/2023	No	No