Contemporary Clinical Trials 47 (2016) 228–234

Contents lists available at ScienceDirect

Contemporary Clinical Trials

journal homepage: www.elsevier.com/locate/conclintrial

A randomized controlled trial on the benefits and respiratory adverse effects of morphine for refractory dyspnea in patients with COPD: Protocol of the MORDYC study

C.A. Verberkt [a,*], M.H.J. van den Beuken-van Everdingen [b], F.M.E. Franssen [c], C.D. Dirksen [d], J.M.G.A. Schols [a,e], E.F.M. Wouters [c,f], D.J.A. Janssen [b,c]

[a] Department of Health Services Research, Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands
[b] Centre of Expertise for Palliative Care, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands
[c] CIRO, Centre of Expertise for Chronic Organ Failure, Horn, The Netherlands
[d] Department of Clinical Epidemiology and Medical Technology Assessment, CAPHRI School for Public Health and Primary Care, Faculty of Health, Medicine and Life Sciences, Maastricht University,Maastricht, The Netherlands
[e] Department of Family Medicine, Maastricht University, Maastricht, The Netherlands
[f] Department of Respiratory Medicine, Maastricht University Medical Centre (MUMC+), Maastricht, The Netherlands

ARTICLE INFO

Article history:
Received 6 November 2015
Received in revised form 18 January 2016
Accepted 23 January 2016
Available online 26 January 2016

Keywords:
Chronic Obstructive Pulmonary Disease
Dyspnea
Morphine
Research protocol
Clinical effectiveness
Adverse effects

ABSTRACT

Dyspnea is one of the most reported symptoms of patients with advanced Chronic Obstructive Pulmonary Disease (COPD) and is often undertreated. Morphine has proven to be an effective treatment for dyspnea and is recommended in clinical practice guidelines, but questions concerning benefits and respiratory adverse effects remain. This study primarily evaluates the impact of oral sustained release morphine (morphine SR) on health-related quality of life and respiratory adverse effects in patients with COPD. Secondary objectives include the impact on exercise capacity, the relationship between description and severity of dyspnea and the presence of a clinically relevant response to morphine, and cost-effectiveness.

A single-center, randomized, double blind, placebo controlled intervention study will be performed in 124 patients with COPD who recently completed a comprehensive pulmonary rehabilitation program. Participants will receive 20–30 mg/24 h morphine SR or placebo for four weeks. After the intervention, participants will be followed for twelve weeks. Outcomes include: the COPD Assessment Test, six minute walking test, Multidimensional Dyspnea Scale and a cost diary. Furthermore, lung function and arterial blood gasses will be measured. These measures will be assessed during a baseline and outcome assessment, two home visits, two phone calls, and three follow-up assessments. The intervention and control group will be compared using uni- and multivariate regression analysis and logistic regression analysis. Finally, an economic evaluation will be performed from a societal and healthcare perspective. The current manuscript describes the rationale and methods of this study and provides an outline of the possible strengths, weaknesses and clinical consequences.

1. Introduction

Chronic Obstructive Pulmonary Disease (COPD) is a chronic, often progressive disease and a major cause of morbidity and mortality [1,2]. Dyspnea is one of the most frequently reported symptoms in patients with advanced COPD and many patients remain breathless despite optimal treatment of their COPD [3,4]. Previously was shown that opioids can reduce refractory dyspnea [5–7] and therefore current (inter)national guidelines recommend opioids as palliative treatment for refractory dyspnea [8,9]. Despite these recommendations, only 2% of the outpatients with advanced COPD are using opioids [3]. Physicians mention uncertainty about benefits, fear for respiratory adverse effects and lack of evidence-based guidelines as main reasons for their reluctance to prescribe opioids [10–12]. Furthermore, a previous study suggests that one-third of patients don't show an improvement in dyspnea when treated with oral morphine for three months [7]. Currently, literature is insufficient to overcome the barriers towards opioid prescription for dyspnea.

Abbreviations: 6MWT, six minute walking test; CAT, COPD Assessment Test; COPD, Chronic Obstructive Pulmonary Disease; EQ-5D-5L, 5-Level version of EuroQol-5 Dimensions; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; GOLD, Global initiative for Obstructive Lung Disease; HRQL, health-related quality of life; IC, inspiratory capacity; MDP, Multidimensional Dyspnea Profile; mMRC, Modified Medical Research Council Dyspnea Scale; MORDYC, MORphine for DYspnea in COPD study; morphine SR, sustained release morphine; NRS, Numeric Rating Scale; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; $PtcCO_2$, transcutaneous pressure of carbon dioxide; SpO_2, pulse oximetric saturation; TLC, total lung capacity.

* Corresponding author.
E-mail address: c.vandenberg@maastrichtuniversity.nl (C.A. Verberkt).

http://dx.doi.org/10.1016/j.cct.2016.01.007
1551-7144/

While opioids can relieve dyspnea in patients with COPD, the effects on health-related quality of life (HRQL) and exercise capacity remain unknown. The aim of palliative care interventions is to improve HRQL [13], but the effect of opioids on HRQL has only been assessed in three RCT's [14–16]. Consequently, a recent systematic review concerning opioid treatment for dyspnea concluded that a meta-analysis of HRQL could not be performed due to study heterogeneity and insufficient data [17]. Further, the effect of opioids on exercise capacity is unclear. In fact, two meta-analyses found no effect on exercise capacity [5,17], mainly due to the administration of small and single doses [18], while a recent study suggested a positive effect on exercise capacity in COPD [19].

Another reported barrier is fear for respiratory adverse effects [10–12]. Data from patients with COPD are limited and results are conflicting. RCT's with low dose morphine showed no relevant effects on respiratory rate, blood gases or oxygen saturation. However, these studies were not designed to assess safety [14,16,20]. On the other hand, high dose oral morphine during exercise caused increased carbon dioxide levels and decreased oxygen levels in patients with COPD [21]. A recent population-based prospective cohort study showed that lower doses of opioids were not associated with increased mortality, while higher doses of opioids were associated with increased mortality, independent of partial pressure of CO_2 [22].

Furthermore, there is no consistent evidence of which patients do and don't benefit from opioid treatment [18]. Johnson et al. [23] showed that older age and more severe dyspnea predict the response to opioids. The American Thoracic Society describes three sensory descriptors of dyspnea which may be linked by specific physiological processes: sensations of work/effort, tightness, and air hunger/unsatisfied inspiration [24]. To date it remains unknown whether these descriptors predict a clinical response to morphine. Finally, the cost-effectiveness of morphine treatment in patients with COPD is not yet known.

To conclude, morphine is an effective treatment for dyspnea and is recommended in current guidelines. However, questions concerning benefits and respiratory adverse effects remain. Furthermore, only two-thirds of the patients benefit from morphine treatment. Knowledge about these benefits and respiratory adverse effects is lacking and should be complemented to improve treatment for patients with COPD.

2. Objectives

The MORphine for DYspnea in COPD (MORDYC) study is designed to investigate the benefits and respiratory adverse effects of oral sustained release morphine (morphine SR) treatment in patients with COPD. This study primarily aims at:

1.1. studying whether and to what extent oral administration of morphine SR improves HRQL in patients with COPD;
1.2. exploring whether and to what extent oral administration of morphine SR leads to respiratory adverse effects in patients with COPD.

The secondary objectives of the study are:

2.1. to investigate the effect of oral administration of morphine SR on exercise capacity in patients with COPD;
2.2. to study the relationship between severity and description of dyspnea and the response to oral administration of morphine SR in patients with COPD;
2.3. to analyze the cost-effectiveness of oral administration of morphine SR in patients with COPD.

We hypothesize that morphine SR improves HRQL and exercise capacity, does not lead to respiratory adverse effects and is cost-effective in patients with COPD. Furthermore, we hypothesize that patients with more severe dyspnea are more likely to respond to morphine SR. Finally, we hypothesize that the description of dyspnea (work/effort, tightness, and air hunger/unsatisfied inspiration) may predict the response to morphine SR.

The objective of this article is to describe the rationale and methods of the MORDYC study and to provide an outline of the possible strengths, limitations and clinical consequences.

3. Methods and analysis

3.1. Design

The MORDYC study is a single-center, randomized, double blind and placebo-controlled intervention study of morphine SR in outpatients with COPD, followed by a prospective cohort study in the same group of patients. A treatment period of four weeks will be sufficient to show results of treatment with morphine SR. Since a time horizon of four weeks may be insufficient to obtain valid estimates of the cost-effectiveness of the use of morphine SR, the collection of data on costs, health status and side effects is prolonged for twelve weeks. However, from an ethical perspective, four weeks is considered to be the maximum period to withhold the placebo group from recommended treatment. Therefore, after the intervention period of four weeks, participants can decide themselves if they will be treated with morphine.

3.2. Study population

The study population will consist of adults with a confirmed diagnosis of COPD based on the Global initiative for Obstructive Lung Disease (GOLD) [1]. Participants are eligible to participate when they experience severe to very severe impairment due to dyspnea (modified Medical Research Council (mMRC) Dyspnea grade 3 or 4) [25] despite optimal pharmacological and non-pharmacological treatment of their COPD [1]. According to the latest GOLD strategy, optimal pharmacological treatment for patients with high symptom burden includes treatment with a combination of a long-acting muscarinic antagonist and a long-acting β-agonist [1], while optimal non-pharmacological treatment includes recent completion of a comprehensive pulmonary rehabilitation program [1,26]. All participants will be recruited at CIRO, a center of expertise for chronic organ failure in Horn, The Netherlands. This center offers a state-of-the-art interdisciplinary pulmonary rehabilitation program, including education, psychosocial counseling, physical exercise training, nutritional counseling, occupational therapy, and exacerbation management, consistent with the latest American Thoracic Society/European Respiratory Society Statement on Pulmonary Rehabilitation [27]. The program at CIRO is patient-tailored lasting for 8 weeks (inpatient) or 14 weeks (outpatient).

Patients will be excluded from this study if they: are aged under 18; are not able to read or fill out the questionnaires or diary; are awaiting lung transplantation; have a history of medicine misuse; use irreversible MAO blockers or opioids; have an allergy for morphine or its constituents; are pregnant or have the potential to get pregnant; have a history of convulsions; or suffer from renal failure (creatinine clearance < 15 ml/min), a head injury, intestinal obstruction, gastroparesis or liver disease. When a potential participant has suffered an exacerbation within two weeks before inclusion, enrolment will be postponed until two weeks after completion of the treatment for this exacerbation.

3.3. Intervention

Participants in the intervention group will receive morphine SR 10 mg capsules, administered twice daily (20 mg/24 h). The control group will receive placebo capsules, which are identical in look and taste to the intervention medication. This ensures that both the participants and study staff won't be able to distinguish the morphine and placebo capsules. Morphine and placebo will be prescribed for four weeks, while meanwhile usual clinical care is continued. The dose can be increased to three times per day 10 mg (30 mg/24 h) after one or two weeks in non-responders. A non-responder is defined as a