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SHORT COMMUNICATION

Study Design and Rationale of "A Multicenter, Open-Labeled, Randomized Controlled Trial Comparing MIdazolam Versus MOrphine in Acute Pulmonary Edema": MIMO Trial

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Abstract
Purpose Morphine has been used for several decades in cases of acute pulmonary edema (APE) due to the anxiolytic and vasodilatory properties of the drug. The non-specific depression of the central nervous system is probably the most significant factor for the changes in hemodynamics in APE. Retrospective studies have shown both negative and neutral effects in patients with APE and therefore some authors have suggested benzodiazepines as an alternative treatment. The use of intravenous morphine in the treatment of APE remains controversial.
Methods The MIdazolan versus MOrphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE. The MIMO trial will evaluate as a primary endpoint whether intravenous morphine administration improves clinical outcomes defined as in-hospital mortality. Secondary endpoint evaluation will be mechanical ventilation, cardiopulmonary resuscitation, intensive care unit admission rate, intensive care unit length of stay, and hospitalization length.
Conclusions In the emergency department, morphine is still used for APE in spite of poor scientific background data. The data from the MIMO trial will establish the effect—and especially the risk—when using morphine for APE.

Keywords Morphine · Mortality · Heart Failure · Benzodiazepines

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Introduction

The use of intravenous morphine in the treatment of acute pulmonary edema (APE) remains controversial. The European Society of Cardiology heart failure (HF) guidelines advocate the use of intravenous morphine with a class of recommendation IIb and level of evidence B [1]. In contrast, the American Heart Association/

American College of Cardiology HF guidelines do not mention morphine in their guidelines from 2013, which reserve this therapy only for palliative care of end-stage HF patients [2].

Major concerns with morphine use include the following:

1. Venodilation in the extremities has been demonstrated, but the volume of blood sequestered by this mechanism is trivial [3].
2. Pulmonary artery end diastolic pressure was not reduced following morphine administration in patients with acute myocardial infarction and APE [4].
3. Potential elevated mortality risk in patients receiving morphine [5–7].
4. Morphine has side effects, including myocardial depression, which can reduce perfusion, and nausea and vomiting, which produce catecholamine release and increased afterload. Sedation is considered a side effect that may be more safely achieved with a benzodiazepine that does not cause nausea or hypotension [8].

Providing sedation to improve the patients' comfort is an integral component of care for nearly every APE with severe dyspnea and anxiety. For decades, benzodiazepines such as midazolam have been the most commonly administered sedative drugs for these patients [9, 10]. However, these types of drugs have not been tested properly in this clinical situation. Nevertheless, it is interesting because benzodiazepines have shown to be efficient anxiolytics over a longer period of time, in addition to the fact that they have positive cardiovascular effects [11]. In two literature reviews, benzodiazepines were recommended for the treatment of chest pain due to anxiolytic properties, and these authors proposed that benzodiazepines could be an alternative to morphine in the treatment of APE [8, 11].

Methods

The MIdazolan versus MOrphine in APE trial (MIMO) is a multicenter, prospective, open-label, randomized study designed to evaluate the efficacy and safety of morphine in patients with APE. The study is approved by an Institutional Review Board or Independent Ethics Committee and authorized by the Spanish Agency of Medicines. The protocol of the trial has been registered at http://www.clinicaltrials.gov (NCT 02856698). The study design algorithm in this study is summarized in Fig. 1.

Study Objectives

The primary objective of MIMO is to assess the safety and benefits of intravenous morphine in patients with APE. The MIMO trial will evaluate as a primary endpoint whether intravenous morphine administration improves clinical outcomes defined as in-hospital mortality. Secondary endpoint evaluation will be mechanical ventilation, cardiopulmonary resuscitation, intensive care unit admission rate, intensive care unit length of stay, and hospitalization length. The study will be performed in accordance with the ethical principles stated in the Declaration of Helsinki in 1964, as revised in Brazil in 2013. The authors will be responsible for the trial design and execution, related statistical analyses, and all aspects of manuscript preparation, including drafting, editing, and decisions on final content.

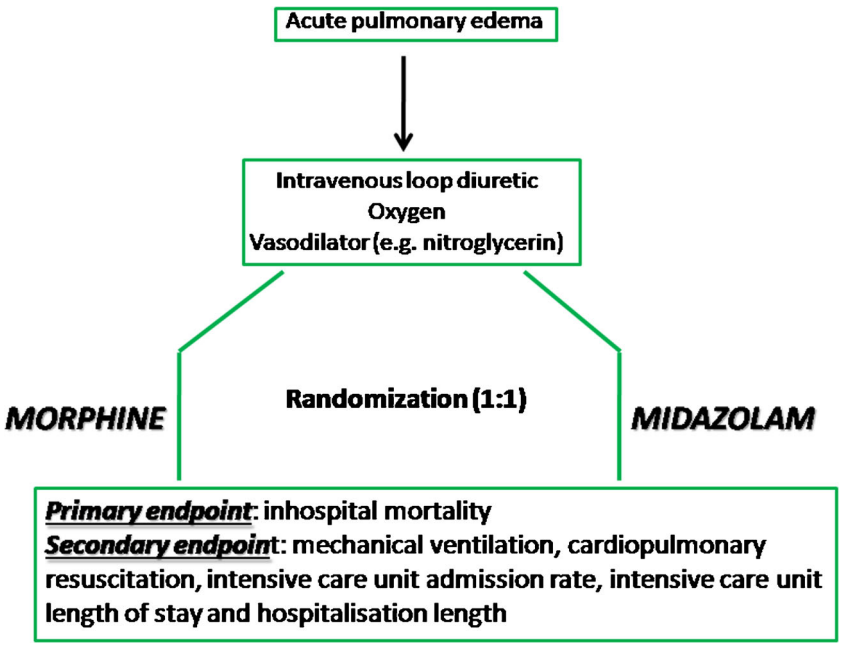

Fig. 1 The MIMO trial algorithm

Study Population

This study will include APE patients with severe dyspnea and anxiety who are ≥18 years of age and have the ability to acknowledge verbally the risks in receiving morphine or midazolam. Exclusions include known severe liver or renal disease defined as levels of aspartate aminotransferase >500 IU/l or creatinine clearance <30 ml/min per 1.73 m^2, respectively, and if they are patients with expectation of death from other illnesses during the course of the trial.

Study Design

Subjects will be randomly assigned to one of two treatment groups in a 1:1 ratio of morphine or midazolam, using a four block-randomization scheme via a web-based computerized program. The company responsible for this procedure will be "onmedic Network" (http://www.onmedic.com). After the investigator has obtained the patient's consent, each patient will be identified using a linkable patient identification code, and will be along with relevant information according to his or her eligibility. Patients and investigators will be aware of the treatment allocation.

Morphine will be administered intravenously in dosages of 2–4 mg that may be repeated if the patient continues suffering from severe anxiety or distress caused by APE until a total dose of 8 mg has been given [8, 12]. In contrast, midazolam will be administered intravenously in dosages of 1 mg that may be repeated if the patient continues suffering from severe anxiety or distress caused by APE until a total dose of 3 mg has been given [10]. All patients will receive standard therapy including intravenous bolus of loop diuretics, oxygen, and/or other vasoactive medications as determined by the investigator [1]. Monitoring of standard of care will be done throughout the trial by the Executive and Steering Committees. Investigators and study coordinators will be provided with feedback reports indicating the percentage of patients at their local sites that received guideline-based care and potential ways to deliver optimal care based on clinical practice guidelines [1].

Sample Size Calculation

A retrospective analysis of the Acute Decompensated HF National Registry (ADHERE) which enrolled hospitalized patients with treatment for, or a primary discharge diagnosis of, acute decompensated HF was used for sample size calculation [6]. There were 147,362 hospitalizations in ADHERE, 20,782 of whom (14.1%) received morphine and 126,580 (85.9%) did not. Patients who received morphine showed a greater mortality (13.0 vs 2.4%). The sample size is determined for the primary end point of the trial by a power analysis with reasonable clinical and statistical assumptions. We estimate that 136 patients (68 patients per group) is needed to have an 80% power at a two-sided type I error of 5% to detect a statistically significant difference between both groups. The intention is to continue the study until the target number of endpoints is achieved, unless there is a recommendation for early termination of the study. An independent data safety monitoring board (DSMB) that includes one cardiologist and two pharmacologists will monitor the trial. The DSMB will receive the results of one blinded interim analysis performed after 68 inclusions. Interim safety analyses will assess all-cause mortality in both study groups. The DSMB will be entitled to make recommendations to the steering committee regarding the continuation of the study.

Statistical Analysis

The primary efficacy analyses will be on an intent-to-treat population. First, we will evaluate the distribution (by Kolmogorov-Smirnov goodness of fit test) and test for homogeneity (using the C-variances test). The data will be analyzed by parametric (Student t test) or nonparametric statistics (Mann-Whitney U test), as appropriate. For normally distributed variables, mean ± SD will be presented. Otherwise, median values will be given. Categorical variables will be summarized as numbers or percentages and compared using the χ^2 or Fisher's exact test, as appropriate. To evaluate independent associations, parameters associated with a p value <0.05 will be identified and examined in multivariate linear regression or multivariate logistic regression models with forced entry of age and sex. In forward selection models, the p value for inclusion of the variables will be set at <0.05. Skewed variables will be logarithmically transformed when appropriate, or dichotomized into the upper third versus the lower two thirds.

There will be one planned interim efficacy analysis carried out using data from the first 50% of enrolled patients. The interim analyses will be conducted for the primary measure of efficacy as well as safety to determine if there is strong evidence of efficacy, clear lack efficacy, or safety concerns for the active treatment. O'Brien-Fleming stopping boundaries will be generated for this interim analysis in which the primary endpoint will be compared between treatment and control group with a nominal one-sided p value of 0.025 [13]. Statistical analyses will be performed using the SPSS 15.0 (SPSS Inc., Chicago, IL, USA) and EPIDAT 3.1 (Area of Health Analysis and Information Systems; World Health Organization).

Study Organization

The study will be conducted under the leadership of an Executive Committee that will be overall responsible for protocol design, study conduct, and publication. The Steering Committee will be responsible for ensuring that the study

enrollment deadlines are met, and that data collection is performed according to accepted practices. The DSMB will monitor the progress of the study and ensure that the safety of the subjects enrolled in the study is not compromised.

The Hospital Universitario de Canarias will serve as the coordinating center for the study and will oversee all activities including clinical operations, data management and statistics. The first patient will be enrolled in December 2016, and enrolment is estimated to continue through 2017.

Discussion

The MIMO trial is designed to provide a definitive estimate in the balance of risk and benefit of morphine treatment in APE. The common rationale for using morphine in APE is based on the presumptive beneficial hemodynamic effects and its theoretical value for managing anxiety and agitation via its sedative properties [14]. Morphine is proposed to reduce preload and, to a lesser extent, afterload (systemic vascular resistance), and to decrease heart rate. Some authors have reported that it may decrease dyspnea while reducing sympathetic nervous system activation [15]. It is hypothesized that these effects may cause a significant reduction in the patient's oxygen demand [15].

In a retrospective study from 2008 based on the ADHERE registry, morphine given in acute decompensated HF was an independent predictor of increased hospital mortality, with an odds ratio of 4.8 (95% CI 4.52–5.18, $p < 0.001$) [6]. This study is limited by its retrospective and observational nature, and, moreover, the authors not performing propensity score analysis. In another retrospective study from 2011 conducted in Israel, in 2336 acutely decompensated HF patients, 9.3% received intravenous morphine [5]. The authors demonstrated that the use of intravenous morphine was independently associated with increased in-hospital death in the multivariable analysis (odds ratio of 2 [95% CI 1.1–3.5], $p = 0.02$), but after performing propensity score analysis, intravenous morphine use was no longer associated with increased mortality (odds ratio of 1.2 [95% CI 0.6–2.5]) [8]. More recently, our group conducted a retrospective study in Spain with a total of 991 acute decompensated HF patients, of which 16.2% received intravenous morphine. We demonstrated that the use of intravenous morphine was independently associated with increased in-hospital mortality in a multivariable analysis (odds ratio of 1.8 [95% CI 1.1–3.1], $p < 0.001$). However, one limitation of our study was that we did not perform a propensity score analysis [7]. An important limitation in the studies cited above was lack of clarity on the dosing and timing of morphine administration.

Although morphine is used in the emergency department for APE, it is necessary to evaluate risks and benefits of this therapy with a randomized controlled study.

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Compliance with Ethical Standards

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Conflict of Interest The authors declare that they have no conflict of interest.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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