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Effect of substitution of intravenous infusion of fentanyl by enteral methadone on the time of weaning from mechanical ventilation in critically ill patients in intensive care units for adults

Submission date	Recruitment status	[ ] Prospectively registered
20/06/2011	No longer recruiting	[ ] Protocol
Registration date	Overall study status	[ ] Statistical analysis plan
29/06/2011	Completed	[ ] Results
Last Edited	Condition category	[ ] Individual participant data
25/02/2016	Respiratory	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Mechanical ventilation is a method where a machine called a ventilator is used to assist or replace spontaneous breathing. Patients undergoing mechanical ventilation are frequently given prolonged and/or high doses of opioid drugs. When this stops, this can cause a withdrawal syndrome and difficulty in weaning from mechanical ventilation (reducing breathing support until the patient can breathe spontaneously). The aim of this study is to test whether giving patients methadone when weaning them from sedation and analgesia (painkillers) decreases the time it takes to wean them from mechanical ventilation.

Who can participate?
Critically ill adult patients undergoing mechanical ventilation and being treated with the painkiller fentanyl intravenously (delivered into a vein).

What does the study involve?
Participants are randomly allocated to one of two groups. For one group intravenous fentanyl is replaced with enteral methadone (enteral means that the drug is given by a tube placed in the nose, stomach or intestine). The other group undergo a gradual reduction of intravenous fentanyl. The duration of ventilation weaning, duration of mechanical ventilation, length of intensive care unit (ICU) stay and length of hospital stay are assessed in both groups.

What are the possible benefits and risks of participating?
The risks to participants are related to the side effects of methadone.

Where is the study run from?
Adult Intensive Care Units of four general hospitals in southern Brazil in the City of Joinville: Hospital Municipal São José, Centro Hospitalar Unimed, Hospital Dona Helena and Hospital Regional Hans Dieter Schmidt.

When is the study starting and how long is it expected to run for?
April 2005 to October 2009

Who is funding the study?
Sao Jose Municipal Hospital (Brazil)

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
N/A

Study information

Scientific Title
Replacement of fentanyl infusion by enteral methadone decreases the weaning time from mechanical ventilation: a randomized controlled trial

Study objectives

The introduction of enteral methadone during weaning from sedation and analgesia in critically ill adult patients on MV would decrease the weaning time from mechanical ventilation (MV)

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Ethics in Research of Hospital Municipal São José of Joinville, 15/10/2004, ref: 008
2. Ethics Committee for Review of Research Projects of Hospital of the Medical College of Medicine, University of Sao Paulo, 29/03/2006, ref: 0195/07

Study design
Prospective multicentre controlled randomized double-blind clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled 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
Mechanical ventilation in critically ill adult patients

Interventions
The enrolled patients were randomized into two groups: the methadone group (MG), for whom intravenous fentanyl was replaced with enteral methadone; and the control group (CG), who underwent a gradual reduction of intravenous fentanyl.
1. The MG received the following treatment:
1.1. One capsule of methadone (10 mg) was administered enterally every 6 hours
1.2. The rate of fentanyl infusion was reduced by 20%
1.3. After 24 hrs, the vial of fentanyl infusion was replaced by the study solution (placebo) and the infusion rate was reduced by 20%
1.4. The infusion rate for the placebo solution was reduced by 20% every 24 hours
2. The following schedule was applied for the CG:
2.1. A placebo capsule was administered enterally every 6 hrs
2.2. The rate of fentanyl infusion was reduced by 20%
2.3. After 24 hrs, the vial of fentanyl was replaced by the study solution (fentanyl) and the infusion rate was reduced by 20%
2.4. The infusion rate for the fentanyl solution was reduced by 20% every 24 hrs
3. Occasional episodes of intolerance to opioid withdrawal, characterized by agitation, anxiety,

tremors, myoclonus, vomiting, diarrhea, piloerection, sweating, dilated pupils, tachycardia and hypertension, were treated with supplemental opioids as follows:
3.1. Bolus 1-2 g/kg of fentanyl
3.2. Increase the capsule dose (methadone/placebo) by 50%
3.3. Increase the infusion rate of the solution (fentanyl/placebo) to the previous dose

The study solutions and capsules were handled, identified and released by a pharmacist, who was the only person that knew the nature of the administered drugs. The capsules contained starch or 10 mg of methadone and were indistinguishable in appearance. The solutions contained 100ml of saline or 50ml of saline and 50ml of fentanyl, also indistinguishable by sight.

The main variables assessed were the following: duration of ventilation weaning (weaning success was defined as 48 hours without reinstitution of mechanical ventilation), duration of mechanical ventilation, length of intensive care unitc (ICU) stay and length of hospital stay. The clinical and demographic data collected included age, sex, weight, indications for hospitalization, comorbidities (hypertension, diabetes mellitus, chronic lung disease, psychiatric and neurological disorders, obesity, alcoholism, smoking or illicit drug use), the information necessary to calculate the Acute Physiology And Chronic Health Evaluation (APACHE) II and deaths before and after discharge from the ICU. Also recorded were the following factors: need for supplemental doses of fentanyl for the treatment of opioid withdrawal intolerance, accumulated doses of fentanyl and midazolam maleate used before the start of weaning and the use of other sedatives.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Methadone, fentanyl

Primary outcome measure
Duration of ventilation weaning (weaning success was defined as 48 hrs without reinstitution of mechanical ventilation)

Secondary outcome measures
1. Duration of mechanical ventilation
2. Length of ICU stay
3. Length of hospital stay

Overall study start date
29/04/2005

Completion date
19/10/2009

Eligibility

Key inclusion criteria

1. The subjects studied were severely ill patients who required MV and the continuous use of fentanyl and who met the following inclusion criteria:
1.1. MV for at least five days
1.2. The use of fentanyl analgesia in varying doses for at least five day or
1.3. A dose of fentanyl more than or equal to 5 µg/kg/h for at least 12 days.
2. Subjects were also required to meet the following ventilation weaning criteria:
2.1. Reversal of the process that caused the respiratory failure
2.2. Adequate oxygenation (PaO2/FiO2) > 200
2.3. Positive end-expiratory pressure (PEEP) less than or equal to 5; FiO2 less than or equal to 0.4 and pH more than or equal to 7.25
2.4. Hemodynamic stability (with minimal or no vasoactive drugs) and neurological stability (ability to initiate respiratory effort)

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
75 patients were randomized

Key exclusion criteria
1. Patients younger than 18 years
2. Patients with terminal diseases
2. Patients with cervical spinal cord injuries or neuromuscular diseases

Date of first enrolment
29/04/2005

Date of final enrolment
19/10/2009

Locations

Countries of recruitment
Brazil

Study participating centre
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Sponsor information

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ROR
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Funder(s)

Funder type
Hospital/treatment centre

Funder Name
Sao Jose Municipal Hospital (Brazil)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration