Open randomized clinical trial to compare pain relief between low-dose methoxyflurane and standard of care for the treatment of patients with trauma pain in emergency medical services in the Netherlands

Published: 11-12-2018
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Primary Objective: This study aims at evaluating efficacy (in terms of superiority to) of low-dose methoxyflurane versus standard of care in the treatment of acute pain due to extremity injuries in the emergency medical services in the Netherlands....

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON50181

Source
ToetsingOnline

Brief title
Low-dose MEOF vs SoC for trauma pain in emergency medical services

Condition

- Other condition

Synonym
trauma pain

Health condition

pijn ten gevolge van trauma

Research involving
Human

Sponsors and support

Primary sponsor: Mundipharma
Source(s) of monetary or material Support: Mundipharma Pharmaceuticals B.V.

Intervention

Keyword: acute pain relief, inhaled analgesia, Methoxyflurane, trauma

Outcome measures

Primary outcome

Change in mean pain intensity (NRS) over 10 min:

Change from baseline (t=0; first *in study* pain (NRS) assessment on scene) to

3, 5 and 10 min using Mixed-Effect Model Repeated Measure (MMRM).

Secondary outcome

Change in mean pain intensity (NRS) over 5 min

Change from baseline (t=0; first in study pain (NRS) assessment on scene), to 3

and 5 min using Mixed-Effect Model Repeated Measure (MMRM).

Speed of onset of analgesia

Time from ambulance arrival to first clinically relevant pain relief (*30%

reduction calculated from baseline (t=0; first in study pain (NRS) assessment

on scene, 3, 5 and 10 min pain (NRS) measurements). Time is calculated from

reported arrival time and reported time of pain measurements.

Proportion of patients with a clinically meaningful reduction in pain intensity

score

Evaluation of the proportion of patients with a clinically meaningful reduction in pain NRS-score (NRS>30% pain relief compared to baseline) at 10 minute calculated from baseline (t=0 first in study pain (NRS) assessment on scene) and t=10 min pain (NRS) measurements.

Satisfaction regarding convenience, treatment efficacy and adverse events

Patients*and Investigator*s satisfaction regarding convenience, treatment efficacy and adverse events will be measured using a 7-item Likert scale in which the respondent will be asked to evaluate the medication administered after 10 min.

Fulfilment of expectations

Patient and investigators* fulfilment of expectations will be measured with a 5-items Likert scale after 10 min.

Patients*Global Impression of Change

Patients* Global Impression of Change with the treatment at discharge time will be measured using a 7-items Likert scale after 10 min.

Treatment costs of pain relief

Standard treatment cost of pain relief will be calculated. A calculation will be made calculating the cost of a 1-point reduction in pain NRS score and the costs of obtaining clinically relevant pain relief (30% reduction in pain NRS

score) will be calculated in both arms.

Health care resource consumption will be measured considering e.g. use of medication, materials, use of monitoring, on scene time as well as transportation costs. Use of materials, medication and monitoring, as well as on scene time and transportation will be based on patient records.

Safety

All AEs and ADRs reported from verbal consent to end of follow up for IMP and SoC treatment unless, in the opinion of the investigator or designated physician, the AE constitute components of the underlying injury. Patients will be asked to document AEs or ADRs of the IMP or SoC treatment in a patient diary for the 14 day post-dose period.

Study description

Background summary

The prevalence of trauma pain is high and if untreated, trauma pain may have a great burden on the patient and result in unnecessary stress and suffering. The stress response to
prolonged pain can cause the appearance of unwanted psychological and physiological events that may interfere with the healing process and prolong patient recovery. Therefore, it is of utmost importance that the effective analgesia is quickly administered, in order to maximise patient satisfaction and recovery and to improve the chances of quicker patient discharge1-4,6 Desirable characteristics for an analgesic in pre-hospital and emergency care are: rapid onset of analgesia, sufficient duration of action, good tolerability and few side effects; efficacy for many different kinds or pain in different populations; ease of storage and administration; and the ability of the patient to self-administer and control the dose. Unlike other available analgesic choices, low-dose methoxyflurane possesses many of these desirable characteristics, as it is rapidly acting, can last for up to an hour if inhaled intermittently or around 20-30 minutes if inhaled continuously. Furthermore, it

provides effective analgesia for different kinds of trauma pain, causes few side effects, is small and simple to use/store, and the patient is able to control the dose administered7.
Despite the fact that low-dose methoxyflurane has been marketed in Australia and New Zealand for the treatment of emergency pain due to trauma for over 40 years, no randomized clinical trials in the emergency medical services (EMS) evaluating its analgesic effectiveness compared to standard of care have been published.
This study however, will be the first study comparing the analgesic efficacy of low-dose methoxyflurane with standard of care in emergency medical services in the Netherlands.
In the Netherlands most used painkillers in the EMS are IV paracetamol, IN/IV fentanyl and IV ketamine. This study will establish the efficacy of low-dose methoxyflurane compared with current standard of care in the Dutch Emergency Medical Services.

Study objective

Primary Objective: This study aims at evaluating efficacy (in terms of superiority to) of low-dose methoxyflurane versus standard of care in the treatment of acute pain due to extremity injuries in the emergency medical services in the Netherlands.

Secondary Objective(s): Evaluating the analgesic effectiveness (proportion of patients with a clinically relevant reduction of the pain score), speed of onset of analgesia, ease of use, time on scene, transportation costs and safety

Study design

Randomized, open label*, controlled trial in the emergency medical services.

*It is not possible to arrange a double-blind study, due to control arm (Standard of Care (SoC)). Within SoC there are multiple treatment options that can be adapted to the situation on scene.

Intervention

Low-dose MEOF:
Patients will be supplied with an inhaler containing 3 mL low-dose MEOF, (99.9%) The trained Emergency Medical Services nurse of the dedicated research team will train the patient to self-administer MEOF.

Study burden and risks

Low-dose methoxyflurane has been administered as an analgesic for over 30 years in Australia and is currently approved for marketing in over 15 countries

worldwide, including Australia, New-Zealand, and the majority of Europe. In the majority of Europe it has been approved for the emergency relief of moderate to severe pain in conscious adult patients with trauma and associated pain.
Serious dose-related nephrotoxicity has only been associated with methoxyflurane when used in high doses over prolonged periods during general anaesthesia. No nephrotoxicity has been observed following methoxyflurane when used under currently approved low-dose.
Therefore for use within the approved indication and in this study setting in line with the approved indication, it is estimated that the risk of treatment is limited.
The patient has the benefit of obtaining effective patient controlled analgesia for different kinds of trauma pain with a rapid-acting non-opioid. Furthermore, MEOF causes few side effects and is small and simple to use/store. The overall benefit for health care is the collection of more clinical data evaluating the place and role of low-dose methoxyflurane as first-line analgesic and compare it with current standard treatment protocols in the Emergency Medical Services.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patients should be * 18 years of age and competent to participate in the study according to the Investigator*s opinion.
2. Moderate pain (NRS0-10 *4 and *8) secondary to extremity injuries
3. Conscious patients with a stable circulation

Exclusion criteria

A potential subject who meets any of the defined criteria will not be eligible for participation in this study and will be treated according to SoC. These criteria will be judged by the Investigator prior to study participation and will be based on (hetero)anamnesis. The defined criteria are:
1. Known hypersensitivity to MEOF or any fluorinated anaesthetic.
2. Personal or family history of malignant hyperthermia.
3. Patients with known liver disease and patients who have a history of showing signs of liver damage after previous MEOF use or halogenated hydrocarbon anaesthesia
4. Known clinically significant renal impairment
5. Known pregnant or likely to be pregnant women at the time of inclusion.
6. Clinically evident cardiovascular instability
7. Clinically evident respiratory depression
8. Treatment with analgesia (with the exception of oral WHO-step 1 analgesics) prior to arrival of the EMS to reduce pain caused by the trauma.
9. Altered level of consciousness due to any cause, including head injury, drugs or al-cohol
10. Active alcohol or drug abuse and/or history of opioid abuse
11. Degenerative diseases, mental illness or other conditions that could affect ability of valuing pain intensity
12. Patients unable to understand the purpose of the study and perform self-assessments, following investigator*s criteria.
13. Participation in another clinical trial within 30 days prior to randomization.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	06-12-2019
Enrollment:	300
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Penthrox
Generic name:	methoxyflurane

Ethics review

Approved WMO Date:	11-12-2018
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	08-07-2019
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	10-03-2020
Application type:	Amendment

Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	METC Brabant (Tilburg)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-001601-82-NL
CCMO	NL65859.028.18