Clinical study report synopsis

Report based on the Final Dissertation to obtain the title of specialist in Emergency Medicine of Dr Reine Sandrine Mendeuka, Université Libre de Bruxelles, Academic year 2022-2023.

Name of sponsor	CHU Brugmann
Name of finished product	PENTHROX® 99,9%
Name of active ingredient	METHOXYFLURANE 99.9%
Title of the study	Prospective monocentric randomized study: use of Methoxyflurane via a mouth-nose mask versus inhaler in the management of pain following limb trauma
Principal Investigator	Dr Reine Sandrine Mendeuka
Study centre	CHU Brugmann Anesthesiology Department 4 Place Arthur Van Gehuchten 1020 Brussels
EudraCT number	2022-002944-40
Publications	Final Dissertation to obtain the title of specialist in Emergency Medicine - Dr Reine Sandrine Mendeuka Université Libre de Bruxelles Academic year 2022-2023
Phase of development	IV
Studied period	Study start: 23/11/2022 Study end: 25/05/2023

Objectives

Methoxyflurane (MTF), marketed under the brand name Penthrox®, is an analgesic belonging to the fluorinated hydrocarbon group of analgesics. It has been used in low doses as an auto-inhaled analgesic for moderate to severe pain. It is self-administered via a Penthrox® inhaler, therefore avoiding the need for an intravenous line. Patients can assess their own pain level and inhale the amount of Penthrox® required for adequate pain relief. The effect is rapid, occurring within 5-10 minutes.

However, inhalation of MTF by mouth via the Penthrox® inhaler requires the inhaler to be held in the patient's hand during aspiration. This can pose problems for certain patients due to a lack of understanding, a lack of coordination or a trauma to the limb holding the inhalator in the mouth. Our study therefore aims to administer Penthrox® via another medical device enabling inhalation of the product via a face mask covering the mouth and nose.

Primary Objective:

Compare the analgesic efficacy of Methoxyflurane administered either by aerosol (nebulizer face mask, experimental arm) versus inhaler (active comparator arm).

Secondary Objective :

Compare the kinetics of pain using these two modes of admission.

Methodology

Prospective, monocentric, single-blind, randomized interventional study with two parallel groups.

Number of patients (planned and actual)
Planned: 60
Actual: 21

Main inclusion criteria
- Admission in the Emergency Department of the CHU Brugmann Hospital
- Acute trauma to the limbs (upper and/or lower)
- ≥18 years
- Patients unable to hold the inhaler optimally
- Minimum Glasgow: 15

Main exclusion criteria
- Hemodynamic instability
- Pregnancy/breastfeeding
- Known allergy to Methoxyflurane
- Respiratory failure
- Hepatic insufficiency
- Chronic renal failure
- Tracheostomy and tracheotomy
- Confusion

Protocol was only applied if Verbal Numeric Rating Scale for pain was >5.

Investigational product, dose, mode of administration
PENTHROX® 99,9% (Medical Developments NED B.V)
Active ingredient : Methoxyflurane 99,9 %.
Pharmaceutical form: Inhalation vapor, liquid
Routes of administration: Inhalation use

Modes of administration:

- Experimental arm: with an aerosol mask which contains a FiltaNeb, Cirrus 2 Nebulizer Kit, with Intersurgical EcoLite™ adult mask without vent, filter and 2.1m hose. Penthrox® (3ml) is placed on blotting paper in a nebulizer receptacle. Once the blotter is soaked with the medication, the mask is placed on the patient's nose and mouth and the patients breathes into the mask at his/her own pace, without aerolization of the product.

- Active comparator arm: with the Penthrox® inhalator
Penthrox® comes in the form of a single-use device. The liquid methoxyflurane (3ml, 1 vial) is added to the inhalator via a one-way valve and is absorbed by a polypropylene wick. Once the liquid is absorbed, it vaporizes and the patient inhales the vapor through the mouthpiece. The patient exhales again into the mouthpiece so that the exhaled methoxyflurane is captured by a charcoal chamber to prevent leakage in the room.

Dose:
No more than 3 ml of Methoxyflurane 99.9% (1 vial) to be administered either by the inhalator or by the SideStream mask.

Duration of treatment
The patient remained in the study for the duration of his/her stay in the Emergency Department. Pain was assessed for a maximum duration of 60 minutes.
If the patient was still experiencing pain after 15 minutes, another analgesic was administered.

Criteria for evaluation
Primary endpoint
Measurement of pain with a Verbal Numeric Rating Scale (VNRS) at 5, 15, 30 and 60 minutes after administration.
Due to the rapid action of Penthrox®, the 5 minutes value is the preferred endpoint.

Statistical method
The characteristics of the participants included in this study were determined using descriptive statistics. Qualitative variables were described using absolute and relative frequencies, while quantitative variables were described in terms of median and interquartile range.
Comparisons of variables according to the route of administration of our substance of interest were made using Fisher's exact test and the Wilcoxon-Mann-Whitney test.
The Wilcoxon-Mann-Whitney test was also used to assess possible differences between the medians of the VNRS scale at each time interval. Data were collected and analyzed using R studio and Excel. The significance level was 5%.

Results

The evaluation of the efficacy of Penthrox® according to the mode of administration (inhalation or aerosol) was carried out on 20 participants. They were allocated to each arm of the study by randomization. Descriptive characteristics of our study population are presented below. Statistical tests show that the study population is homogeneous.

Table 1

Descriptive characteristics - Demographics	
Arms	**Total (n=20)**
Experimental arm (nebulizing aerosol mask)	10 (50%)
Active comparator arm (inhalator)	10 (50%)

Gender			
	Aerosol (n=10)	**Inhalator (n=10)**	**Total (n=20)**
Female	5 (50%)	3 (30%)	8 (40%)
Male	5 (50%)	7 (70%)	12 (60%)
	p value: 0.6		

Age			
	Aerosol (n=10)	**Inhalator (n=10)**	**Total (n=20)**
	53.5 [40.0-65.0]	38.0 [21.8-44.8]	44,0 [30.8 – 63.5]
	p value: 0.2		

Trauma types			
	Aerosol (n=10)	**Inhalator (n=10)**	**Total (n=20)**
Pelvis contusion	2 (20%)	1 (10%)	3 (15%)
Shoulder contusion	1 (10%)	0 (0%)	1 (5%)

Fractured ankle	1 (10%)	2 (20%)	3 (15%)
Fractured shoulder	0 (0%)	1 (10%)	1 (5%)
Fractured humerus	2 (20%)	2 (20%)	4 (20%)
Fractured leg	0 (0%)	1 (10%)	1 (5%)
Fractured foot	0 (0%)	1 (10%)	1 (5%)
Hip contusion	1 (10%)	0 (0%)	1 (5%)
Shoulder luxation	2 (20%)	2 (20%)	4 (20%)
Wrist contusion	1 (10%)	0 (%)	1 (5%)
	p value > 0.9		

Descriptive characteristics – Patient satisfaction			
	Aerosol (n=8)	**Inhalator (n=10)**	**Total (n=18)**
Yes	8 (100%)	10 (100%)	18 (100%)
No	0 (0%)	0 (0%)	0 (0%)

Data missing for 2 out of 20 patients (n=18)

Adverse events – IMP side effects	n=20[1]		
	Aerosol (n=10)	**Inhalator (n=10)**	**Total (n=20)**
Euphoria	0 (0%)	1 (10%)	1 (5%)
Headache	1 (10%)	0 (0%)	1 (5%)
No side effects	7 (70%)	6 (60%)	13 (65%)
Drowsiness	1 (10%)	2 (20%)	3 (15%)
Dizziness	1 (10%)	1 (10%)	2 (10%)
	p value > 0.9		

Values presented as: n (%)
Age values presented as: median, [interquartile range]
p value: arm comparison (aerosol vs inhalator) according to Fisher exact test or Wilcoxon-Mann-Whitney test

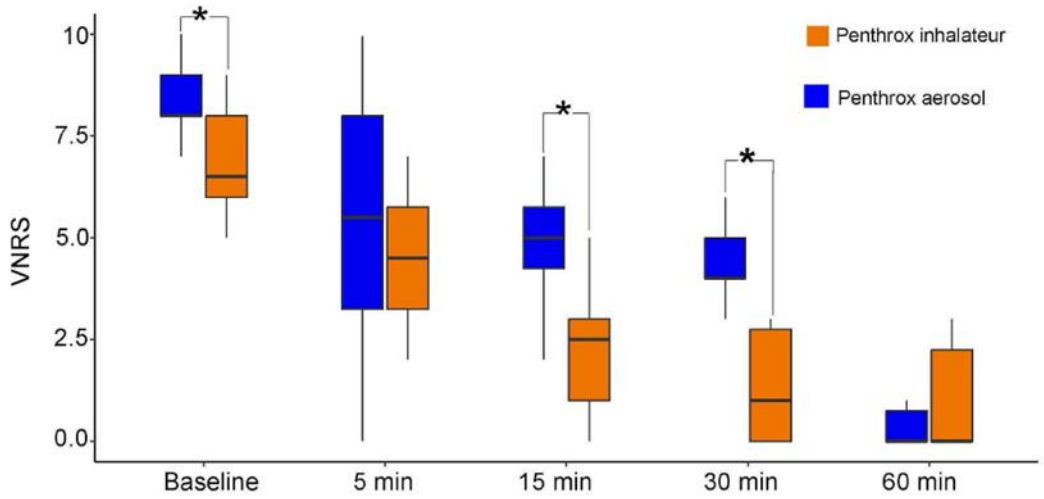
The results of the temporal analysis of the pain perception (VNRS pain scale) according to the route of administration are reported below.

Pain levels are different between groups at the start of the study.
There is no significant difference in pain level between groups after 5 minutes. However, at the 15 minutes and 30 minutes timepoints, pain reduction is significantly higher in patients who received Penthrox® by means of its inhalator (classic route of administration). After one hour, both groups showed a statistically significant improvement in pain levels, irrespective of the route of administration.

Table 2

Analysis of repeated measurements (over time) of VNRS			
Time (min)	Aerosol	Inhalator	p-value
0	8.0 [8.0-9.0]	6.5 [6.0-8.0]	0.0354
5	5.5 [3.2-8.0]	4.5 [3.2-5.8]	0.4693
15	5.0 [4.2-5.8]	2.5 [1.0-3.0]	0.0045
30	4.0 [4.0-5.0]	1.0 [0.0-2.8]	0.0017
60	0.0 [0.0-0.8]	0.0 [0.0-2.2]	0.9255

values presented as: median, [interquartile range]



Study limitations

- Very small sample size (preliminary results)
- Pain assessment is subjective. It differs from one patient to another.

Conclusion

Methoxyflurane is an effective analgesic with few side effects. It is simple to use in an Emergency Room to relieve acute pain.

This study shows that methoxyflurane used in an aerosol mask provides good analgesia, albeit less quickly that the methoxyflurane used with its original inhalator.

It remains however an acceptable solution for patients who cannot use the inhalator correctly.

Date of report

15/07/2024