**Title page**

**Title:** Inhaled methoxyflurane provides greater analgesia and faster onset of action versus standard analgesia in patients with trauma pain. InMEDIATE: a randomized controlled trial in Emergency Departments

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**Abstract**

**Objective:** The InMEDIATE study aimed to evaluate the change in intensity of traumatic pain in adult patients treated with methoxyflurane versus standard analgesic treatment in Spain, and is the first randomized, active-controlled, multicenter trial of methoxyflurane in the emergency setting in Europe.

**Methods:** Randomized, controlled study that enrolled adult patients with acute moderate to severe (score ≥4 on the 11-point Numeric Rating Scale [NRS]) trauma-associated pain in 14 Spanish emergency departments. Patients were randomized 1:1 to methoxyflurane (up to 2×3mL) or standard analgesic treatment (SAT). Co-primary endpoints were the change from baseline in NRS pain intensity over the first 20 min of treatment and time to first pain relief.

**Results:** 305 patients were randomized (methoxyflurane: 156; SAT: 149). Most patients in the SAT group (70%) received intravenous first-step analgesics and 9.4% of patients were treated with opioids. Mean decrease from baseline in NRS pain intensity was greater for methoxyflurane than SAT at all time points, with a significant treatment difference overall up to 20 min (repeated measures model: 2.47 vs. 1.39; treatment difference: 1.00; 95% CI: 0.84, 1.32). Median time to first pain relief was significantly shorter for methoxyflurane than SAT (3 vs. 10 min). Methoxyflurane achieved better patient and clinician ratings for pain control and comfort of treatment than SAT and exceeded patient/clinician expectations of treatment in 77%/72% of cases compared with 38%/19% for SAT.

**Conclusions:** These results support consideration of methoxyflurane as a non-narcotic, easy to administer, rapid-acting, first-line alternative to currently available analgesic treatments for trauma pain.

**Keywords:** Acute pain, analgesic, emergency department, trauma, methoxyflurane, Penthrox

**Trial registration:** EudraCT: 2017-000338-70; ClinicalTrials.gov: NCT03256903.

## Introduction

*Background*

Pain is the most frequent complaint of patients visiting the Emergency Department (ED), yet undertreatment of acute pain (oligoanalgesia) in the emergency setting remains widespread.[1-5] In addition to improving patient comfort and satisfaction,[6] effective pain management aids mobilization and subsequent treatment of the patient, leading to shorter hospital stays.[7] Reasons for suboptimal pain management in the emergency setting may include underassessment of pain, time/resource constraints, lack of training, aversion to opioid analgesia, patient reluctance, and limitations of currently available treatments (particularly in the prehospital environment) such as requirement for intravenous (IV) placement, limited efficacy of weak analgesics, and impracticality of nitrous oxide.[8]

Methoxyflurane is a volatile fluorinated hydrocarbon that was first used as an inhalation anesthetic (Penthrane®, Abbott Laboratories) in the 1960s.[9] Its use was generally discontinued by the late 1970s due to reports of nephrotoxicity at high anesthetic doses caused by metabolism of methoxyflurane and release of fluoride ions[10-12] and in 2005 the US Food and Drug Administration determined a final withdrawal to prevent new drug applications for methoxyflurane for anesthesia.[13] Methoxyflurane has well documented analgesic properties at low doses and has continued to be widely used in Australia and New Zealand (administered via a disposable inhaler; Penthrox®, Medical Developments International, Scoresby, Australia) since the 1970s for emergency relief of trauma-associated pain and procedural analgesia.[14-16] With over 40 years of clinical use as an analgesic in Australia, methoxyflurane has an established safety profile. There have been no reports of nephro- or hepato-toxicity in clinical studies of analgesic methoxyflurane and no clinically significant effect on systolic blood pressure, pulse rate, respiratory rate, or consciousness levels has been observed.[16] The most common adverse events are mild and transient

dizziness and somnolence.[17] Penthrox has recently been approved in Europe and other territories including Latin America, South Africa and Eastern Europe for the emergency relief of moderate to severe pain in conscious adult patients with trauma-associated pain.[18]

Clinical and observational studies show that at low analgesic doses, methoxyflurane is not associated with renal adverse events.[19-21] The safe upper limit of exposure to methoxyflurane has been determined as 2 minimum alveolar concentration (MAC) hours, which gives a serum fluoride level of 40 µmol/L.[19] The maximum recommended analgesic dose of 6 mL/day or 15 mL/week results in exposure of 0.59 methoxyflurane MAC-hours, which gives a safety margin for analgesic use of 2.7- to 8-fold.[19]

Low-dose methoxyflurane analgesia is intended for short-term pain relief in the emergency setting.[17] It is non-narcotic, portable, provides rapid pain relief (within 4-5 min[20,22]) and its effects are quickly reversible, meaning that it does not limit subsequent treatment options and can also be used as a bridging agent until additional analgesia is prescribed. Methoxyflurane is provided in 3 mL vials with a green whistle-shaped single-use inhaler (Penthrox), is not a narcotic drug and does not require any special storage conditions. Once added to the inhaler, the methoxyflurane liquid is absorbed by a polypropylene wick, vaporizes and is inhaled by the patient through the mouthpiece. The inhaler includes an activated charcoal chamber (AC) which adsorbs exhaled methoxyflurane when the patient exhales back into the mouthpiece, preventing occupational exposure. Stronger analgesia can be achieved by occlusion of the diluter hole on the AC chamber with a finger. One inhaler (3 mL methoxyflurane) provides 25 to 30 minutes of analgesia with continuous inhalation; intermittent use extends the duration of action up to at least 1 hour[23] and a second 3 mL dose can be administered if required.[17]

*Importance*

The European approval of low-dose methoxyflurane analgesia in 2015 was based on the results of a Phase III randomized, placebo-controlled study in 300 patients in UK EDs (STOP!), which showed a significantly greater reduction in pain scores and high patient and healthcare professional satisfaction ratings for methoxyflurane.[20,22] However, with the exception of two studies versus intramuscular tramadol,[24,25] there is currently a lack of comparative data for methoxyflurane versus other analgesic agents from randomized controlled trials (RCTs), mainly in EDs.

*Goals of This Investigation*

The InMEDIATE study (Inhaled Methoxyflurane: Pain relief in adult trauma patients in Spain [in Spanish: Inhalado MEtoxifluorano: alivio del Dolor en pacIentes Adultos con Trauma en España]) was designed as a pragmatic trial to compare the pain relief achieved with methoxyflurane versus standard analgesic treatment (SAT) in patients with acute moderate to severe pain due to trauma in Spanish EDs (prehospital and hospital).[26] There is currently a lack of guidelines or harmonized pain protocols in Spain and current clinical practice includes a variety of analgesic agents. SAT was thus defined as the analgesic protocol at each site, to enable comparison of methoxyflurane with the most representative daily clinical practice comparator group. To our knowledge, this is the first active-controlled RCT of methoxyflurane for the emergency treatment of trauma pain in Europe. The study aimed to investigate whether the change in pain intensity over the first 20 min of treatment was greater with methoxyflurane than standard analgesia in adult patients with acute traumatic pain.

## Methods

### Study Design and Setting

InMEDIATE was a Phase IIIb, randomized, active-controlled, open-label, parallel group trial performed in 14 EDs (including one prehospital emergency unit) in Spain from 07 July 2017 to 02 April 2018. After screening and eligibility assessments (including recording of medical/surgical history, concomitant medication, injury type and pain assessment), patients were randomized 1:1 to receive methoxyflurane or SAT, with a safety follow-up visit on-site or via telephone at 14±2 days after discharge for collection of adverse event (AE) data and a blood sample for laboratory safety analysis (where possible). The primary objective was to evaluate the change in pain intensity in patients treated with methoxyflurane versus SAT. The study was designed by the coordinators of the Pain Group of the Spanish Society of Emergency Medicine and representatives of the Spanish Clinical Research Network (SCReN). Operational tasks and statistical analysis were performed by SCReN. The study was conducted in accordance with International Council for Harmonization Good Clinical Practice adhering to the ethical principles of the Declaration of Helsinki.

Patients provided written informed consent before the pre-study screening examination and administration of study treatment. Most screening assessments were part of normal triage, therefore except for obtaining consent, there was no delay to treatment caused by enrolment in the study. Patients were informed about the study by a member of the research team who verbally explained the study procedures, characteristics of the medicinal product and its possible adverse effects and provided the patient with written information (see Web Appendix 1). Considering the potential distraction of patients by pain, the information sheet was designed to be short and simple, and investigators were trained through "role-play" in requesting consent from people with pain in emergencies. Ethics approval was obtained from the Clinical Research Ethics Committee of La Paz University Hospital and the Spanish

Agency of Medicines and Medical Devices, and the study is registered in the European Clinical Trials Database (EudraCT: 2017-000338-70) and ClinicalTrials.gov (NCT03256903). Full protocol details have previously been published.[26]

*Selection of Participants*

Patient eligibility was established by the treating physician in the ED. Conscious patients aged ≥18 years with moderate to severe pain (pain score ≥4 on the 11-point Numeric Rating Scale [NRS]) secondary to trauma who were not expected to require surgery or hospitalization for ≥12 hours were eligible. Exclusion criteria included use of any other analgesic for the acute traumatic pain, contraindications to methoxyflurane administration as per the Summary of Product Characteristics[17] (hypersensitivity to methoxyflurane or any fluorinated anesthetic, malignant hyperthermia, evidence of liver damage after previous methoxyflurane or halogenated hydrocarbon anesthetic use, clinically significant renal impairment, altered level of consciousness due to any cause including head injury, drugs or alcohol, clinically evident cardiovascular instability or respiratory depression) or contraindications to any of the drugs included in the site's analgesic protocol, pregnancy, participation in another clinical trial within the previous 30 days and medical conditions that could have affected the patient's ability to complete self-assessments of pain intensity.

It was planned to randomize a total of 310 patients (155 per treatment group). The sample size calculation was performed using 2.5% significance levels and 90% power for testing of both primary endpoints (Bonferroni method). Assuming a treatment difference of 20% in favor of methoxyflurane for both primary endpoints (based on results of the STOP! study),[20,22] 147 evaluable patients per treatment arm were required (see Web Appendix 2). 310 patients were planned to allow for a drop-out/non-evaluable rate of 5.5%.

*Interventions*

Patients were randomized to methoxyflurane or SAT. The randomization sequence was created using SAS® version 9.4 (SAS Institute Inc., Cary, NC, USA) statistical software procedure 'PROC PLAN' with a 1:1 allocation. No randomization seed was specified. Lists of 30 patients per treatment group were created for the complete sample size (310 patients), a total of 60 patients per site. Ten blocks were created per site, each one included six treatments. Randomization lists were used to generate sealed envelopes that were distributed to sites to perform randomization.

Study treatment was administered by research staff as soon as possible after randomization. Patients randomized to the methoxyflurane group received one Penthrox inhaler containing 3 mL methoxyflurane. Investigators and research staff were trained on administration of methoxyflurane during an initial investigators' meeting, and later retrained during site initiation visits. Research staff showed patients how to use the device and the diluter hole, and instructed them to inhale continuously to start with, followed by intermittent inhalation, depending on analgesic need. A second inhaler was provided if required, with a maximum methoxyflurane dose of 2 x 3 mL. Patients randomized to the SAT group received the standard analgesic treatment for patients with moderate to severe trauma-associated pain according to the analgesic protocol of the treating ED. Although there was variation between sites, standard analgesic treatment most frequently comprised non-steroidal anti-inflammatory drugs (NSAIDs) for moderate pain and IV non opioid and opioid analgesics for severe pain (see Web Appendix 3). Any type of analgesic administered via any route was valid. Analgesics administered after Time 0 in either group were considered as rescue medication. Patients in both treatment groups could request rescue medication at any time.

*Measurements and Outcomes*

The investigators recorded the time of medical attention, randomization and the start of treatment and any rescue medication use. Each patient was provided with a paper case report form on which they recorded their pain intensity using the 11-point NRS (where 0=no pain and 10=unbearable pain) before the start of study treatment (baseline), at 3, 5, 10, 15, 20 and 30 min after the start of study treatment and at the time of discharge. Further assessments were performed at 40, 50 and 60 min after the start of treatment (if the patient was still in the ED) to assess the maintenance of analgesia. Patients were provided with a pre-programmed tablet ("alerting device") that was activated by study staff when the patient commenced treatment (Time 0). The alerting device sounded an alarm at the times when patients had to record their pain intensity. Two other buttons were programmed on the tablets that were pressed when the patient felt the first pain relief and the first meaningful pain relief, respectively; the patient also recorded their pain intensity score at those times. Patient outcome measures were assessed at 30 min after the start of treatment and included patient and clinician satisfaction with treatment (rating pain control, comfort of treatment administration and AEs on an NRS scale where 0=not at all satisfied and 10=completely satisfied), patient and clinician fulfillment of expectation regarding pain control (evaluated using the CEP scale,[27] a 5-point Likert scale) and patients' global impression of change (PGIC), evaluated using the PGIC scale,[28] a Likert scale with seven choices to answer the question "*From the beginning of treatment, how would you describe the change (if there is any change) in your activity limitation, symptoms, emotions and global life quality in relation to your pain?*".

The co-primary efficacy endpoints were the change in NRS pain intensity over the first 20 min of treatment, and time from the start of treatment to first pain relief (as subjectively

reported by the patient). Other study endpoints are detailed in the protocol publication.[26] It was originally planned to also analyze time-to-event endpoints from the time of randomization,[26] but the final analyses were performed only from the start of treatment, to avoid possible center bias due to variability in the speed of dispensing and treatment administration.

AEs observed by the investigator or spontaneously reported by the patient were recorded throughout the study up to the follow-up visit on Day 14±2. Vital signs were measured and the patient's degree of sedation was recorded using the Ramsay scale at baseline and 30 min after the start of treatment. A blood sample was taken for hematological analysis (complete blood count: red blood cells, hemoglobin, hematocrit, mean corpuscular volume, platelets, leukocytes and differential count) and biochemical analysis (aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, gamma-glutamyl transferase, total bilirubin, blood urea nitrogen, calcium, chloride, sodium, potassium, creatinine, glucose, total protein and albumin) before or within 1 hour of the start of treatment and at the follow-up visit, where possible.

*Analysis*

The primary endpoint of the change in pain intensity measured using the NRS scale from baseline to 3, 5, 10, 15 and 20 min was analyzed using a mixed model repeated measures analysis of covariance that included fixed-effect terms for treatment and time, and baseline NRS pain intensity. Estimates (differences or ratios) and 2-sided 95% confidence intervals (CIs) for the treatment effect were obtained for each time point. The co-primary endpoint of time to first pain relief was analyzed using time-to-event methodology, including a Cox Proportional Hazards model with treatment and qualifying pain intensity at randomization as

fixed effects, center as a random effect and baseline NRS pain intensity as a covariate. Kaplan-Meier estimates for the median time to first pain relief and median time to first meaningful pain relief were provided. When pain relief occurred in the interval [0,t], it was considered as an event, otherwise this time was considered as censored. Secondary efficacy endpoints were analyzed in an exploratory manner. Dichotomous and categorical variables were analyzed using contingency tables with the chi-squared or Fisher's exact test, as appropriate. Qualitative variables were analyzed using a Student's t-test or analysis of variance, as appropriate. SPID15 was calculated as the cumulative sum of the differences from baseline in NRS pain intensity at each time point to 15 min after the start of treatment.

The primary analysis population was the intention-to-treat (ITT) population, with supportive analyses performed on the per-protocol (PP) population (randomized patients who met the eligibility criteria, did not receive rescue medication, and completed primary pain intensity assessments). Safety analyses were performed using the safety population, which included all patients who received at least one dose of study treatment. No missing data imputation or adjustments for multiplicity were performed. Statistical calculations were performed under the statistical environment R using RStudio editor (R version 3.4.0 [2017-04-21]).[29] R package lmerTest was used to analyze mixed model estimations.[30] Statistical code was run with a random seed fit to 123789 to allow reproducibility and produced a pdf document providing answers to the points presented in the statistical analysis plan.

## Results

*Characteristics of Study Patients*

A total of 305 patients were randomized and treated (156 in the methoxyflurane group and 149 in the SAT group, Figure 1) and all were analyzed for efficacy (ITT population) and

safety. Seven patients were excluded from the PP population (due to incomplete CRD [three patients], AEs [two patients], inability to inhale, and patient requesting discharge due to disappearance of pain). All remaining patients had complete pain intensity records up to and including the 30 min time point. Efficacy results were very similar for both the ITT and PP populations; therefore, only results for the ITT population are presented. Demographic characteristics were comparable in both treatment groups (Table 1). Most patients presented with orthopedic injuries. Patient distribution by site is provided in Web Appendix 4; two patients were enrolled in a prehospital emergency unit and all other patients were enrolled in EDs. The majority of patients in the SAT group received treatment with first-step analgesics (mostly IV); 126 received NSAIDs (mainly dexketoprofen and ketorolac), 11 received metamizole and eight received paracetamol. Five patients received second-step opioid analgesia (IV tramadol) and nine patients received third-step opioids. One patient was treated with mepivacaine (note that some patients received more than one drug as SAT). Eighteen patients received IV diazepam as co-analgesic added to NSAID and one patient received diazepam added to IV fentanyl.

*Efficacy results*

An adjusted repeated measures model showed that the mean reduction from baseline in NRS pain intensity was significantly larger for the methoxyflurane group than the SAT group at all time points, with global reductions over the first 20 min of 2.47 vs. 1.39 (difference: 1.00; 95% CI: 0.84 – 1.32; Table 2 and Figure 2a). The reduction in pain intensity was larger for methoxyflurane than SAT regardless of baseline pain intensity (moderate [NRS 4-<7] or severe [NRS ≥7], Figures 2b and 2c) and class of SAT administered (non-opioid or opioids, Figure 2d). Originally it was planned to analyze pain relief evolution in patients with moderate pain treated with first-step analgesia but considering that almost 80% of randomized patients had severe pain, the analyses based on class of SAT (including all

patients) and baseline pain intensity (independently of the SAT used) were performed instead. Although a significant number of patients were discharged during the hour after start of treatment, the pain relief data are favorable for the methoxyflurane group at all time points (Table 3 and Web Appendix 5).

All time-to-event endpoints were significantly shorter (i.e. more favorable) for methoxyflurane compared with SAT, including median (interquartile range) time to first pain relief (3.17 [1.83, 7.44] vs. 10.00 [5.74, 14.64] min), time to first meaningful pain relief (10.00 [5.00, 16.22] vs. 20.00 [1.03, 29.25] min; Web Appendix 6), time to pain relief ≥2 points on the NRS scale (5.00 [3.00, 10.00] vs. 15.00 [10.00, 27.50] min) and time to maximum pain relief (20.00 [15.00, 30.00] vs. 30.00 [20.00, 30.00 min). The mean (± standard deviation [SD]) NRS pain intensity score was similar for both treatment groups at the time of first pain relief (methoxyflurane: 5.31 [1.84]; SAT: 5.64 [1.58]) and at the time of first meaningful pain relief (methoxyflurane: 3.23 [1.78]; SAT: 3.55 [1.54]).

Results for SPID15 (patient-averaged summed pain intensity difference 15 min after the start of treatment) also showed that methoxyflurane provided significantly greater pain relief than SAT (mean [±SD] -54.13 [27.25] vs. -26.43 [25.83]). The proportion of pain responders (patients with ≥30% improvement from baseline in NRS pain intensity) was significantly higher in the methoxyflurane group than the SAT group (87.9% vs. 57.7%). Similarly, the proportion of patients achieving a decrease in pain intensity to ≤3 points on the NRS was higher in the methoxyflurane group than the SAT group at both 15 min (39.7% vs. 14.0%) and 30 min (62.2% vs. 34.9%).

The number of patients that required rescue medication until discharge was low in both treatment groups (13 patients [8.5%] in the methoxyflurane group and 18 patients [12.1%] in the SAT group). Two patients received opioids as rescue medication in the methoxyflurane group, compared with nine patients in the SAT group. Eight patients (5.1%) in the methoxyflurane group required a second methoxyflurane inhaler.

Median (IQR) scores (on a 0-10 scale) for patient satisfaction with methoxyflurane treatment were 9.00 (8.00, 10.00) for pain control, 9.00 (9.00, 10.00) for comfort of treatment and 9.00 (8.00, 10.00) for safety (AEs), while SAT scored 7.75 (6.00, 9.00), 8.00 (6.38, 9.50) and 9.00 (7.00, 10.00), respectively. Very similar results were obtained for clinician satisfaction with treatment. Methoxyflurane treatment exceeded patients' expectations in 77% of cases compared with 38% for SAT (Figure 3a), while clinicians' expectations were exceeded in 72% of cases for methoxyflurane and 19% for SAT. Higher ratings were also achieved for PGIC in the methoxyflurane group than the SAT group (Figure 3b).

*Safety results*

In the methoxyflurane group, 38 patients (24.4%) reported a total of 48 AEs (44 considered treatment-related) and in the SAT group, eight patients (5.4%) reported a total of nine AEs (four considered treatment-related). The most common AEs in the methoxyflurane group were dizziness (22 patients), somnolence (five patients) and nausea (four patients). Most AEs (77.2%) were mild, 19.3% were moderate and 3.5% (2 events) were severe (treatment-related dizziness in the methoxyflurane group and unrelated pain in the SAT group) and the majority resolved on the same day. Treatment-related AEs are summarized in Table 4. Five patients experienced a total of six serious AEs; all were related to the trauma injury (pain, surgery, hospitalization) and none were fatal or related to study

treatment. Five patients discontinued due to AEs; this included four patients in the methoxyflurane group due to dizziness (two patients), nausea and vomiting (one patient) and verbigeration and dizziness (one patient), and one patient in the SAT group due to surgery. Of note, both methoxyflurane and SAT scored highly (median 9 out of 10) in response to the patient and clinician satisfaction question *"Are you satisfied with the AEs suffered for the treatment"?*

No clinically significant laboratory abnormalities were identified from the baseline (N=302) or follow-up visit (N=188) laboratory safety results (Web Appendix 7). There were no significant differences between methoxyflurane and SAT groups when changes in systolic and diastolic blood pressure (SBP and DBP) and heart rate between baseline and 30 min after the start of treatment were evaluated. Mean (±SD) changes from baseline in the methoxyflurane and SAT groups at 30 min were -3.7 (11.6) vs. -2.2 (13.8) mmHg for SBP, -2.3 (8.6) vs. -0.7 (9.3) mmHg for DBP and -2.7 (8.6) vs. -1.8 (8.7) bpm for heart rate. Full vital signs data are provided in Web Appendix 7. Ramsay sedation scale was evaluated before and 30 min after starting treatment. Almost all patients were scored as Ramsay 2 (cooperative, oriented, tranquil) at both time points; however, in the methoxyflurane arm three patients were scored as Ramsay 1 (anxious, agitated, restless) before treatment and one patient remained at Ramsay 1 after 30 min, and two patients were scored as Ramsay 3 (responsive to commands only) at 30 min.

**Limitations**

This active-controlled study is an important addition to the available data on methoxyflurane, but a limitation is the open-label design which has the potential for patient and investigator bias. A double-blind study would be difficult in the emergency setting given the variation in the route of administration of the SATs (different protocols in each center) and the distinct

odor and unique mode of administration of methoxyflurane. Even employing a double-blind study design with a single comparator treatment, the dispensing and administration of active and placebo treatments via different routes would potentially delay patient treatment with ethical implications where rapid analgesia is required. The fact that the mean (SD) pain intensity was so similar for both treatment groups at the time of first pain relief (methoxyflurane: 5.31 [1.84]; SAT: 5.64 [1.58]) and at the time of first meaningful pain relief (methoxyflurane: 3.23 [1.78]; SAT: 3.55 [1.54]), despite the time to these pain relief endpoints being significantly different between the groups, suggests that the open design does not bias the patient self-evaluation of pain involved in the primary objective of the trial.

Although the majority (68.5%) of patients in the SAT group received IV NSAIDs, there was wide variation in the treatments given as SAT (ranging from weak oral analgesics to strong IV opioid analgesics) due to the differences in analgesic protocols between centers. However, the efficacy analysis included center as a covariate, and furthermore, analysis of the primary endpoint by class of SAT showed that methoxyflurane provided greater pain relief than non opioid and opioid SAT subgroups. We acknowledge that the differing analgesic protocols in Spain compared to the US and the fact that methoxyflurane is not available in the US limit generalizability to the US health care system; however, the study highlights differences between low doses of inhaled methoxyflurane and different treatment protocols mainly based on IV analgesics (both non opioids and opioids).

We recognize that the biochemical analysis in this study was constrained by the relatively long interval to the follow-up sample (14±2 days) and the limited number of follow-up samples obtained (188/305 patients). In practice, patient attendance in person at a follow-up visit in a pragmatic trial in EDs is difficult to achieve, because the reasons for requesting emergency attendance are usually resolved, and patients may live some distance from the ED. Therefore, only one follow-up visit was required in this study, which was set at 14 days (as in the pivotal STOP! study[20,22]) to allow for capture of AEs (specifically renal and liver

dysfunction) after methoxyflurane administration. Multiple blood tests would have been required to capture transient laboratory abnormalities, which was not practical in this study population/setting. Indeed, many patients in our study refused to return to the unit for the single follow-up visit. In any case, comparison of baseline versus follow-up blood test of almost 200 patients showed no cases of renal or hepatic impairment profile or out of range results. Despite historical reports of nephro- and hepato-toxicity with anesthetic doses of methoxyflurane, clinical experience in the emergency setting in Australia and Europe suggests that low analgesic doses of methoxyflurane are not associated with a risk of renal or hepatic AEs,[20-22] although caution is advised when administering to patients with renal or hepatic impairment.[17] Given the emergency setting and the lack of opportunity for follow-up of patients enrolled in this study, electrocardiograms (ECGs) were not performed. However, a previous Phase 1 QT/QTc trial has shown that a single supratherapeutic (12 mL) dose of methoxyflurane did not have an effect on QTc interval above the regulatory threshold of concern or any effect on other ECG parameters.[31] Furthermore, a large observational study of 135,770 patients in the prehospital setting in Australia (of whom 17,629 received methoxyflurane) did not identify any difference in event rates for heart disease between patients who received methoxyflurane and those who did not.[21]

**Discussion**

This pragmatic randomized controlled study in Spanish EDs demonstrated superior pain relief with methoxyflurane compared to the standard analgesic treatments used in daily practice in the Spanish EDs for adult patients with moderate to severe trauma-associated pain. The results of this study are especially relevant given the recent European approval of methoxyflurane for this indication and considering the previous lack of data from RCTs comparing methoxyflurane with an active comparator. Designing an active-controlled trial in this setting is challenging due to variability in the management of trauma pain nationally, regionally and even at the local level within hospitals.[32] In Spain, there is no established standard analgesic treatment or clinical guidelines for the emergency treatment of trauma

pain, thus it was necessary to employ a pragmatic open-label study design. The most frequently used analgesics in Spanish EDs are NSAIDs (generally administered parenterally), with a relatively low level of opioid use.[33,34] This is reflected in the current study, where over two thirds of patients (68.5%) in the SAT group received IV NSAIDs, and only 9.4% received opioid analgesia. Given that NSAIDs are a first-step analgesic,[35] this might be anticipated to lead to more favorable results for methoxyflurane versus SAT than if most patients had received stronger opioid analgesics. However, analysis of the primary endpoint by class of SAT in this study showed a larger mean reduction in pain intensity for methoxyflurane compared to both non opioid and opioid analgesics (Fig. 2d). Previous prospective studies have shown methoxyflurane to provide much larger reductions in pain scores than IM tramadol in the emergency setting,[24,25] and while one large retrospective study found similar efficacy of methoxyflurane and intranasal (IN) fentanyl,[36] a second showed IV morphine and IN fentanyl to both be significantly more effective than methoxyflurane.[37]

The reduction in pain intensity achieved with methoxyflurane treatment in this study is likely to represent a clinically relevant improvement. A ~20% reduction in NRS pain intensity corresponds to 'minimal improvement' in patients with acute pain[38] while a reduction of ≥2 points or 30% is the minimum clinically important difference (MCID) for chronic pain,[39] although the MCID in acute pain varies greatly between studies[40] and is influenced by baseline pain intensity.[38,40] A 30% improvement was achieved by 87.9% of patients in the methoxyflurane group and 57.7% in the SAT group by 20 min. Studies by Todd *et al*[41] and Gallagher *et al*[42] suggesting a change of ~13mm on a 100mm VAS scale to be the MCID for acute pain provide further support for the improvement in pain intensity with methoxyflurane in this study being clinically relevant to the patient. The finding that mean NRS pain intensity was so similar for both treatments at the time of first pain relief provides validation that these time-to-event measures were based on a similar degree of pain reduction in both groups, despite the subjective nature of the evaluation and open-label study design.

Our findings for methoxyflurane treatment are very similar to those reported for the STOP! study adult population,[22] although baseline pain intensity in STOP! was limited to NRS ≤7. The STOP! study demonstrated mean adjusted changes from baseline in VAS pain intensity (0-100 scale) of a similar magnitude to the mean adjusted decreases in NRS pain intensity in this study. Median time to first pain relief (subjectively assessed by the patient) was 5 min in the STOP! study[22] and 3 min in this study.

Both studies showed high treatment satisfaction with methoxyflurane; patients and clinicians in this study scored methoxyflurane 9 or 10 out of 10 for pain control, comfort of treatment and safety, with methoxyflurane exceeding expectations in 77%/72% of cases, while in the STOP! study adult subgroup, methoxyflurane was rated as “Excellent”, “Very good” or “Good” by ~75% of patients, physicians and research nurses.[22] When investigators of this trial were asked to evaluate methoxyflurane characteristics with a scale of 6 categories (from very bad to very good), all evaluated the efficacy, speed and satisfaction as good or very good, and 96% of them also rated patient safety, ease of use, comfort, reduction of anxiety and self-control of analgesia as good or very good.[43]

The consistent results from this study and the STOP! study support the use of methoxyflurane analgesia in the emergency setting. Methoxyflurane shows highly effective analgesia compared to a range of analgesics, with a fast onset of pain relief within a median of 3-5 minutes from the start of treatment. Furthermore, the time required to dispense and administer methoxyflurane is minimal compared with parenteral and/or controlled medications. In this trial, time from randomization to treatment administration was significantly shorter with methoxyflurane than with SAT (median [IQR] 7.00 [4.00, 11.00] min vs. 10.00 [7.00, 18.25] min, respectively). Median (IQR) duration of ED stay was also shorter for methoxyflurane than SAT (median [IQR] 107.00 (86.75, 150.00) min vs. 113.50 [93.00, 142.00] min). The methoxyflurane inhaler is easy to use and well-accepted by patients and

treating healthcare professionals, as evidenced by the high satisfaction with the efficacy, comfort and safety of treatment in this study and the Global Medication Performance results in the STOP! trial.[20,22]

No safety concerns regarding emergency use of methoxyflurane were raised in this study. Consistent with the STOP! study[20,22] and the product SPC,[17] the most frequently occurring AE in the methoxyflurane group was dizziness, reported for 14.1% of patients, followed by somnolence (3.2%) and nausea (2.6%). The incidence of dizziness was notably lower than in the STOP! study adult population (36.3%).[22] All dizziness AEs were transient in nature, resolving the same day, and most were mild in severity. Biochemical and hematologic analysis and vital signs showed no clinically notable changes or differences between the treatment groups.

In conclusion the InMEDIATE trial, the first active-controlled study of methoxyflurane in Europe, showed superior efficacy and speed of action of methoxyflurane versus the standard analgesic treatments usually used in EDs for treating acute trauma-associated pain. Subgroup analyses suggest that methoxyflurane provides good pain relief for both moderate and severe pain, and better pain relief than a range of analgesics from NSAIDs to opioids. However, additional studies versus individual agents are required to fully investigate specific treatment differences. Methoxyflurane may be considered as a non-narcotic, easy to administer, rapid acting, first-line alternative to currently available analgesic treatments for trauma pain.

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**References**

1. Albrecht E, Taffe P, Yersin B, et al. Undertreatment of acute pain (oligoanalgesia) and medical practice variation in prehospital analgesia of adult trauma patients: a 10 yr retrospective study. Br J Anaesth. 2013;110:96-106.
2. Cordell WH, Keene KK, Giles BK, et al. The high prevalence of pain in emergency medical care. Am J Emerg Med. 2002;20:165-169.
3. Mura P, Serra E, Marinangeli F, et al. Prospective study on prevalence, intensity, type, and therapy of acute pain in a second-level urban emergency department. J Pain Res. 2017;10:2781-2788.
4. Tanabe P, Buschmann M. A prospective study of ED pain management practices and the patient's perspective. J Emerg Nurs. 1999;25:171-177.
5. Todd KH, Ducharme J, Choiniere M, et al; PEMI Study Group. Pain in the emergency department: results of the pain and emergency medicine initiative (PEMI) multicenter study. J Pain. 2007;8:460-466.
6. Downey LV, Zun LS. Pain management in the emergency department and its relationship to patient satisfaction. J Emerg Trauma Shock. 2010;3:326-330.
7. Gupta A, Kaur K, Sharma S, et al. Clinical aspects of acute post-operative pain management & its assessment. J Adv Pharm Technol Res. 2010;1:97-108.
8. Dißmann PD, Maignan M, Cloves PD, Gutierrez Parres B, Dickerson S, Eberhardt A. A Review of the Burden of Trauma Pain in Emergency Settings in Europe. Pain Ther. 2018;7:179-192.
9. Tomlin PJ. Methoxyflurane. Br J Anaesth. 1965;37:706-709.
10. Crandell WB, Pappas SG, Macdonald A. Nephrotoxicity associated with methoxyflurane anaesthesia. Anesthesiology. 1966;27:591-607.
11. Mazze RI, Shue GL, Jackson SH. Renal dysfunction associated with methoxyflurane anaesthesia: a randomised, prospective clinical evaluation. JAMA. 1971;216:278-288.
12. Mazze RI. Methoxyflurane revisited: tale of an anaesthetic from cradle to grave. Anesthesiology. 2006;105:843-846.

13. US Federal Register. Determination that Penthrane (methoxyflurane) inhalation liquid, 99.9 percent, was withdrawn from sale for reasons of safety or effectiveness. Available from: https://www.federalregister.gov/documents/2005/09/06/05-17559/determination-that-penthrane-methoxyflurane-inhalation-liquid-999-percent-was-withdrawn-from-sale. Accessed May 17, 2019.
14. Blair HA, Frampton JE. Methoxyflurane: A Review in Trauma Pain. Clin Drug Investig. 2016;36:1067-1073.
15. Jephcott C, Grummet J, Nguyen N, et al. A review of the safety and efficacy of inhaled methoxyflurane as an analgesic for outpatient procedures. Br J Anaesth. 2018;120:1040-1048.
16. Porter KM, Dickerson S, Dayan AD, et al. The role of inhaled methoxyflurane in acute pain management. Open Access Emerg Med. 2018;10:149-164.
17. Penthrox® summary of product characteristics. Available from: https://www.medicines.org.uk/emc/medicine/31391. Accessed May 17, 2019.
18. Medical Developments International. European Penthrox® Update, 12 August 2016. Available from: http://www.medicaldev.com/wp-content/uploads/2016/08/ASX-Announcement_European-Penthrox-Update_120816.pdf. Accessed May 17, 2019.
19. Dayan AD. Analgesic use of inhaled methoxyflurane: Evaluation of its potential nephrotoxicity. Hum Exp Toxicol. 2016;35:91-100.
20. Coffey F, Wright J, Hartshorn S, et al. STOP!: a randomised, double-blind, placebo-controlled study of the efficacy and safety of methoxyflurane for the treatment of acute pain. Emerg Med J. 2014;31:613-618.
21. Jacobs IG. Health effects of patients given methoxyflurane in the prehospital setting: a data linkage study. Open Emerg Med J. 2010;3:7-13.
22. Coffey F, Dissmann P, Mirza K, Lomax M. Methoxyflurane analgesia in adult patients in the Emergency Department: a subgroup analysis of a randomized, double-blind, placebo-controlled study (STOP!). Adv Ther. 2016;33:2012-2031.

23. Oxer HF. Effects of Penthrox® (methoxyflurane) as an analgesic on cardiovascular and respiratory functions in the pre-hospital setting. J Mil Veterans Health. 2016;24:14-20.
24. Konkayev AK, Baymagambetov S, Sainov M, et al. Evaluation of clinical effectiveness of inhalatory analgesic “Penthrox” for pain relief in ankle injuries. Arch Balk Med Union. 2013;48(Suppl 3):239-243.
25. Lim KJH, Koh ZX, Zafirah NA. Clinical evaluation of Penthrox® (methoxyflurane) and tramadol for the Singapore emergency ambulance service. Abstract presented at the Society for Emergency Medicine in Singapore Annual Scientific Meeting; Feb 27-28 2016; Singapore.
26. Borobia AM, Capilla Pueyo R, Casal Codesido JR, et al; InMEDIATE Group. Phase IIIb, open label randomised clinical trial to compare pain relief between methoxyflurane and standard of care for treating patients with trauma pain in Spanish Emergency Units (InMEDIATE): Study protocol. IBJ Clin Pharmacol. 2017;1:e0008.
27. Pujiula-Masó J, Suñer-Soler R, Puigdemont-Guinart M, et al. La satisfacción de los pacientes hospitalizados como indicador de la calidad asistencial. [Satisfaction among hospitalized patients as an indicator of quality of care]. Enfermería clínica 2006;16:1-54.
28. Guy W, editor. ECDEU Assessment Manual for Psychopharmacology. 1976. Rockville,MD, U.S. Department of Health, Education, and Welfare.
29. R Core Team (2018). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/. Accessed May 17, 2019.
30. Kuznetsova A, Brockhoff PB, Christensen RHB. lmerTest Package: Tests in Linear Mixed Effects Models. Journal of Statistical Software 2017;82:1-26.
31. Medical Developments International. “Thorough QT/QTc” Penthrox® Clinical Trial Successfully Meets All Primary and Secondary Objectives, 13 August 2013. Available from: https://www.medicaldev.com/wp-content/uploads/2013/09/MVP-ASX-Announcement-Successful-Clinical-Study-Results1.pdf. Accessed May 17, 2019.

32. Caba Barrientos F, Benito Alcalá MC, Montes Pérez A, et al. Encuesta nacional sobre dolor en las urgencias hospitalarias. [National survey on pain in hospital emergencies]. Rev Soc Esp Dolor. 2014;21:3-15.
33. García-Castrillo Riesgo L, Andrés Gómez M, Rubini Puig S, et al. El dolor en procesos traumáticos agudos leves. [Pain in mild acute traumatic processes]. Emergencias. 2006;18:19-27.
34. Mínguez Masó S, Herms Puig R, Arbonés Aran E, et al. Prevalencia y enfoque terapéutico del dolor en el servicio de urgencias de un hospital Universitario. [Pain prevalence and therapeutic approach in the emergency department of a university hospital.] Rev Soc Esp Dolor. 2014;21:205-11.
35. World Health Organization. WHO's cancer pain ladder for adults 1986. http://www.who.int/cancer/palliative/painladder/en/. Accessed May 17, 2019.
36. Oxer HF, Wilkes G. Methoxyflurane is a safe, easy, effective analgesic for prehospital pain relief. Prehosp Disast Med. 2007;22:s77.
37. Middleton PM, Simpson PM, Sinclair G, et al. Effectiveness of morphine, fentanyl, and methoxyflurane in the prehospital setting. Prehosp Emerg Care. 2010;14:439-447.
38. Cepeda MS, Africano JM, Polo R, et al. What decline in pain intensity is meaningful to patients with acute pain? Pain 2003;105:151-157.
39. Farrar JT, Young JP Jr, LaMoreaux L, et al. Clinical importance of changes in chronic pain intensity measured on an 11-point numerical rating scale. Pain. 2001;94:149-158.
40. Olsen MF, Bjerre E, Hansen MD, et al. Pain relief that matters to patients: systematic review of empirical studies assessing the minimum clinically important difference in acute pain. BMC Med. 2017;15:35. doi:10.1186/s12916-016-0775-3.
41. Todd KH, Funk KG, Funk JP, et al. Clinical significance of reported changes in pain severity. Ann Emerg Med. 1996;27:485-489.
42. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med. 2001;38:633-638.

43. García Collado S, Carballo Cardona C, Capilla Pueyo R, et al. Methoxyflurane as an analgesic for the emergency relief of traumatic pain: A satisfaction survey of health professionals participating in InMEDIATE, a phase IIIb trial. Abstract #14651, presented at the European Emergency Medicine congress, Glasgow, Sep. 8-12, 2018.

**Table 1 Demographic and Baseline Characteristics (Safety Population)**

| Characteristic | | Methoxyflurane N=156 | SAT N=149 |
|---|---|---|---|
| Age (years) | Mean (SD) | 45.2 (18.75) | 45.3 (17.95) |
| | >65 [n (%)] | 33 (21.2) | 26 (17.4) |
| Gender [n (%)] | Female | 80 (51.3) | 69 (46.3) |
| Baseline $NRS_{0-10}$ | Mean (SD) | 7.6 (1.39) | 7.5 (1.46) |
| Pain intensity | ≥7 [n (%)] | 127 (82.5) | 114 (76.5) |
| Number of injuries | Median (IQR) | 1 (1.0 – 2.0) | 1 (1.0 – 2.0) |
| Injury type [n (%)] | Contusion | 87 (55.8) | 87 (58.4) |
| | Fracture | 39 (25.0) | 36 (24.2) |
| | Swelling | 29 (18.6) | 29 (19.5) |
| | Dislocation | 11 (7.1) | 10 (6.7) |
| | Laceration | 2 (1.3) | 3 (2.0) |
| | Burns | 1 (0.6) | 0 |
| Injury site [n (%)] | Lower limbs | 67 (42.9) | 73 (49.0) |
| | Upper limbs | 66 (42.3) | 57 (38.3) |
| | Chest | 20 (12.8) | 24 (16.1) |
| | Neck | 17 (10.9) | 8 (5.4) |
| | Other | 12 (7.7) | 11 (7.4) |
| Joint involvement [n (%)] | | 110 (70.5) | 114 (76.5) |
| | Ankle | 21 (13.5) | 21 (14.1) |
| | Knee | 17 (10.9) | 24 (16.1) |
| | Foot | 15 (9.6) | 21 (14.1) |
| | Wrist | 18 (11.5) | 14 (9.4) |
| | Others | 44 (28.3) | 50 (33.6) |
| SAT treatment[a] [n (%)] | IV non-opioids | - | 104 (69.8) |
| | Oral non-opioids | - | 16 (10.7) |
| | IM non-opioids | - | 14 (9.4) |
| | IV opioids | - | 12 (8.1) |
| | TM opioids | - | 2 (1.3) |

| Characteristic | Methoxyflurane N=156 | SAT N=149 |
|---|---|---|
| Others | - | 1 (0.7) |

IM: intramuscular; IQR: interquartile range; IV: intravenous; N/A: not applicable; NRS: Numeric Rating Scale; NS: not significant; SAT: standard analgesic treatment; SD: standard deviation; TM: transmucosal.

[a] More than one drug could be administered as SAT.

**Table 2 Repeated Measures Analysis of Reduction from Baseline in NRS Pain Intensity Over 20 Minutes After the Start of Treatment (ITT Population)**

| Time point | Adjusted reduction from baseline[a] | | Estimated treatment effect (95% confidence interval) |
|---|---|---|---|
| | Methoxyflurane (N=156) | SAT (N=149) | |
| Overall | 2.47 | 1.39 | 1.00 (0.84 – 1.32) |
| 3 mins | 1.45 | 0.89 | 0.56 (0.30 – 0.82) |
| 5 mins | 1.98 | 1.17 | 0.81 (0.51 – 1.12) |
| 10 mins | 2.62 | 1.33 | 1.28 (0.82 – 1.64) |
| 15 mins | 2.89 | 1.45 | 1.44 (1.07 – 1.80) |
| 20 mins | 3.19 | 1.89 | 1.29 (0.91 – 1.68) |

a From mixed model repeated measures analysis of covariance including fixed-effect terms for treatment and time, and baseline NRS pain intensity.

ITT: intent-to-treat; NRS: Numeric Rating Scale; SAT: standard analgesic treatment.

**Table 3 Improvement from Baseline in NRS Pain Intensity Over 60 Minutes After the Start of Treatment (ITT Population)**

| Time after start of treatment (min) | Methoxyflurane (N=156) | | SAT (N=149) | |
|---|---|---|---|---|
| | n | Mean (95% CI) | n | Mean (95% CI) |
| 3 | 155 | 1.82 (1.58 - 2.06) | 149 | 0.54 (0.35 - 0.73) |
| 5 | 154 | 2.72 (2.45 - 2.99) | 149 | 1.04 (0.79 - 1.29) |
| 10 | 152 | 3.77 (3.45 - 4.09) | 149 | 1.77 (1.48 - 2.06) |
| 15 | 152 | 4.34 (4.01 - 4.67) | 149 | 2.46 (2.13 - 2.79) |
| 20 | 150 | 4.94 (4.62 - 5.26) | 149 | 3.09 (2.73 - 3.45) |
| 30 | 150 | 5.40 (5.06 - 5.74) | 149 | 3.92 (3.57 - 4.27) |
| 40 | 66 | 5.19 (4.72 - 5.66) | 68 | 4.02 (3.52 - 4.52) |
| 50 | 43 | 5.56 (4.97 - 6.15) | 48 | 4.48 (3.89 - 5.07) |
| 60 | 33 | 5.75 (4.98 - 6.52) | 37 | 4.92 (4.19 - 5.65) |

CI: confidence interval; ITT: intent-to-treat; N: total number of patients in population; n: number of patients with evaluable data; NRS: Numeric Rating Scale (0-10 scale); SAT: standard analgesic treatment.

**Table 4 Number of Patients With Treatment-Related Adverse Events (Safety Population)**

| Adverse event | Methoxyflurane (N=156) | | | Standard Analgesic Treatment (N=149) | | |
|---|---|---|---|---|---|---|
| | Definitely related | Probably related | Possibly related | Definitely related | Probably related | Possibly related |
| Concentration loss | 0 | 1 | 1 | 0 | 0 | 0 |
| Dizziness | 5 | 12 | 4 | 0 | 0 | 2 |
| Drowsiness | 0 | 1 | 0 | 0 | 0 | 0 |
| Euphoria | 0 | 1 | 0 | 0 | 0 | 0 |
| Felt faint | 0 | 0 | 1 | 0 | 0 | 0 |
| Forgetfulness | 0 | 1 | 0 | 0 | 0 | 0 |
| Hypersalivation | 0 | 1 | 0 | 0 | 0 | 0 |
| Memory impairment | 0 | 0 | 1 | 0 | 0 | 0 |
| Nausea | 0 | 3 | 1 | 0 | 1 | 0 |
| Oral dryness | 0 | 0 | 1 | 0 | 0 | 0 |
| Oral pruritis | 0 | 1 | 0 | 0 | 0 | 0 |
| Somnolence | 1 | 4 | 0 | 0 | 0 | 0 |
| Tiredness | 0 | 1 | 0 | 0 | 0 | 0 |
| Verbigeration | 0 | 1 | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 2 | 0 | 0 | 1 | 0 |

Events that were considered unlikely to be related to treatment were also considered as related; however, no adverse events were reported in this category.