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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Study objective: The objective of the InMEDIATE study was to evaluate the change in intensity of traumatic pain over the first 20 min in adult patients treated with methoxyflurane versus standard analgesic treatment in Spain. This the first randomized, active-controlled, multicenter trial of methoxyflurane in the emergency setting in Europe.

Methods: This was a randomized, controlled study that enrolled adult patients with acute moderate to severe (score $\geq$4 on the 11-point Numeric Rating Scale) trauma-associated pain in 14 Spanish emergency departments. Patients were randomized 1:1 to methoxyflurane (up to 2×3 mL) or standard analgesic treatment. Coprimary endpoints were the change from baseline in Numeric Rating Scale pain intensity score during the first 20 minutes of treatment and time to first pain relief.

Results: Three hundred five patients were randomized (methoxyflurane 156; standard analgesic treatment 149). Most patients in the standard analgesic treatment group (70%) received intravenous first-step analgesics and 9.4% of patients were treated with opioids. Mean decrease from baseline in Numeric Rating Scale pain intensity score was greater for methoxyflurane than standard analgesic treatment at all points, with a significant treatment difference overall up to 20 minutes (repeated-measures model 2.47 versus 1.39; treatment difference 1.00; 95% confidence interval 0.84 to 1.32). Median time to first pain relief was significantly shorter for methoxyflurane than standard analgesic treatment (3 versus 10 minutes). Methoxyflurane achieved better patient and clinician ratings for pain control and comfort of treatment than standard analgesic treatment and exceeded patient and clinician expectations of treatment in, respectively, 77% and 72% of cases compared with 38% and 19% for standard analgesic treatment.

Conclusion: These results support consideration of methoxyflurane as a nonnarcotic, easy-to-administer, rapid-acting, first-line alternative to currently available analgesic treatments for trauma pain. [Ann Emerg Med. 2020;74:315-328.]

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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 or resource constraints, lack of training, aversion to opioid analgesia, patient reluctance, and limitations of currently available treatments (particularly in the out-of-hospital environment) such as requirement for intravenous

*All members are listed in the Appendix.

Editor's Capsule Summary

What is already known on this topic

Low-dose methoxyflurane inhalation has been used for pain control and procedural sedation in Australia and New Zealand for greater than 40 years without reported toxicity.

What question this study addressed

This randomized pragmatic trial compared methoxyflurane with standard analgesic therapy for trauma-associated pain control during the first 20 minutes of treatment in 13 Spanish emergency departments (EDs).

What this study adds to our knowledge

Investigators found that pain relief for patients in the methoxyflurane treatment group (n=156) was superior compared with that for individuals in the standard therapy group (n=149). The safety profile was acceptable.

How this is relevant to clinical practice

Although not available in the United States, in this study methoxyflurane inhalation is an effective alternative to standard pain control methods in the ED for patients with trauma-associated pain.

line 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, Chicago, IL) in the 1960s.[9] Its use was generally discontinued by the late 1970s because of reports of nephrotoxicity at high anesthetic doses, caused by metabolism of methoxyflurane and release of fluoride ions,[10-12] and in 2005 the 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 through 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 greater than 40 years of clinical use as an analgesic in Australia, low-dose methoxyflurane has an established safety profile. There have been no reports of nephro- or hepatotoxicity 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, Latin America, and South Africa 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–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 minimum alveolar concentration–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 nonnarcotic, is portable, and provides rapid pain relief (within 4 to 5 minutes[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) 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, which adsorbs exhaled methoxyflurane when the patient exhales into the mouthpiece, preventing occupational exposure. Stronger analgesia can be achieved by occlusion of the diluter hole on the activated charcoal 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 3 randomized, placebo-controlled study in 300 patients in UK EDs (STOP!), which showed a significantly greater reduction in pain scores and high patient and health care professional satisfaction ratings for methoxyflurane.[20,22] However, with the exception of 2 studies versus intramuscular tramadol,[24,25] there is currently a lack of comparative data for methoxyflurane versus other analgesic agents from randomized controlled trials, mainly in EDs.

Goals of This Investigation

The Inhaled Methoxyflurane: Pain Relief in Adult Trauma Patients in Spain study (InMEDIATE [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 in Spanish ED patients with acute moderate to severe pain caused by trauma (out-of-hospital and inhospital).[26] There is currently a lack of guidelines or harmonized pain protocols in Spain, and current clinical practice includes a variety of analgesic agents. Standard analgesic treatment was thus defined as the local 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 randomized controlled trial of methoxyflurane for the emergency treatment of trauma pain in Europe. The study aimed to investigate whether the change in pain intensity during the first 20 minutes of treatment was greater with methoxyflurane than standard analgesia in adult patients with acute traumatic pain.

MATERIALS AND METHODS

Study Design and Setting

InMEDIATE was a phase 3b, randomized, active-controlled, open-label, parallel-group trial performed in 13 EDs and 1 out-of-hospital unit in Spain from July 7, 2017, to April 2, 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 standard analgesic treatment, with a safety follow-up visit on site or by telephone at 14 days (SD 2 days) after discharge for collection of adverse event data and a blood sample for laboratory safety analysis (when possible). The primary objective was to evaluate the change in pain intensity in patients treated with methoxyflurane versus standard analgesic treatment. 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. Operational tasks and statistical analysis were performed by the network. 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 prestudy 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 enrollment in the study. Patients were informed about the study by a member of the research team, who explained the study procedures, characteristics of the medicinal product, and its possible adverse effects and provided the patient with written information (Appendix E1, available online at http://www.annemergmed.com). 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. Full protocol details have previously been published.[26]

Selection of Participants

We planned to randomize a total of 310 patients (155 per treatment group). Patient eligibility was established by the treating physician in the ED. Conscious patients aged 18 years or older with moderate to severe pain (pain score $\geq$4 on the 11-point Numeric Rating Scale) as a result of trauma who were not expected to require surgery or hospitalization for greater than or equal to 12 hours were eligible. Exclusion criteria included use of any other analgesic for the acute traumatic pain, contraindications to methoxyflurane administration in accordance with 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 from 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.

Interventions

Patients were randomized to methoxyflurane or standard analgesic treatment. The randomization sequence was created with SAS (version 9.4; SAS Institute, Inc., Cary, NC) 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 including 6 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 1 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, for a maximum methoxyflurane dose of 6 mL (3 mL×2 inhalers). Patients randomized to the standard analgesic treatment group received the standard analgesic treatment for patients with moderate to severe trauma-associated pain, according to the local analgesic protocol of the treating ED. Although there was variation among sites, standard analgesic treatment most frequently comprised nonsteroidal anti-inflammatory drugs for moderate pain and intravenous nonopioid and opioid analgesics for severe pain (Appendix E2, available online at http://www.annemergmed.com). Any type of analgesic administered by any route was valid. Analgesics administered after time 0 in either group were considered rescue medication. Patients in both treatment groups could request rescue medication at any time.

Methods of Measurement and Outcome Measures

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 Numeric Rating Scale (0=no pain and 10=unbearable pain) before the start of study treatment (baseline); at 3, 5, 10, 15, 20, and 30 minutes after the start of study treatment; and at discharge. Further assessments were performed at 40, 50, and 60 minutes after the start of treatment (if the patient was still in the ED) to assess the maintenance of analgesia. Patients were provided with a preprogrammed tablet ("alerting device") that was activated by study staff when the patient commenced treatment (time 0). The alerting device sounded an alarm when patients had to record their pain intensity. Two other buttons were programmed on the tablets; one was pressed when the patient experienced the first pain relief; the other, at first meaningful pain relief. The patient also recorded his or her pain intensity score at those times. Patient outcome measures were assessed at 30 minutes after the start of treatment and included patient and clinician satisfaction with treatment (rating pain control, comfort of treatment administration, and adverse events on the Numeric Rating Scale, in which 0=not at all satisfied and 10=completely satisfied), patient and clinician fulfillment of expectation in regard to pain control (evaluated with the Cuestionario de Expectativas de Pacientes: Patients Expectations questionnaire scale,[27] a 5-point Likert scale), and patients' global impression of change, evaluated with the Patients' Global Impression of Change scale,[28] a Likert scale with 7 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 coprimary efficacy endpoints were the change in Numeric Rating Scale pain intensity score during the first 20 minutes 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] We originally planned to also analyze time-to-event endpoints from randomization,[26] but the final analyses were performed only from the start of treatment to avoid possible center bias caused by variability in the speed of dispensing and treatment administration.

Adverse events observed by the investigator or spontaneously reported by the patient were recorded throughout the study up to the follow-up visit on day 14 (SD 2). Vital signs were measured and the patient's degree of sedation was recorded with the Ramsay Sedation Scale at baseline and 30 minutes after the start of treatment. A blood sample was taken for hematologic analysis (CBC count: RBCs, hemoglobin, hematocrit, mean corpuscular volume, platelets, leukocytes, and differential count) and biochemical analysis (levels of aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, alkaline phosphatase, γ-glutamyl transferase, total bilirubin, blood urea nitrogen, calcium, chloride, sodium, potassium, creatinine, glucose, and total protein and albumin) before or within 1 hour of the start of treatment and at the follow-up visit, when possible.

Primary Data Analysis

The sample size calculation was performed with 2.5% significance levels and 90% power for testing of both primary endpoints (Bonferroni's 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 (Table E1, available online at http://www.annemergmed.com). Three hundred ten patients were planned to allow for a dropout or nonevaluable rate of 5.5%.

The primary endpoint of the change in pain intensity measured with the Numeric Rating Scale from baseline to 3, 5, 10, 15, and 20 minutes was analyzed with a mixed-model repeated-measures analysis of covariance that included fixed-effect terms for treatment and time, and baseline Numeric Rating Scale pain intensity score. Estimates (differences or ratios) and 2-sided 95% confidence intervals for the treatment effect were obtained for each time. The coprimary endpoint of time to first pain relief was analyzed with 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 Numeric Rating Scale pain intensity score 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 an event; otherwise, this time was considered censored. Secondary efficacy endpoints were analyzed in an exploratory manner. Dichotomous and categoric variables were analyzed with contingency tables with the χ^2 or Fisher's exact test, as appropriate. Continuous variables were analyzed with a Student's *t* test or analysis of variance, as appropriate. Patient-averaged summed pain intensity difference 15 minutes after the start of treatment was calculated as the cumulative sum of the differences from baseline in Numeric Rating Scale pain intensity score at each point to 15 minutes after the start of treatment.

The primary analysis population was the intention-to-treat population, with supportive analyses performed on the per-protocol population (randomized patients who met the eligibility criteria, did not receive rescue medication, and completed primary pain intensity assessments). Safety analyses were performed with 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 (version 3.4.0).[29] The 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 Subjects

A total of 305 patients were randomized and treated (156 in the methoxyflurane group and 149 in the standard analgesic treatment group) (Figure 1) and all were analyzed for efficacy (intention-to-treat population) and safety. Seven patients were excluded from the per-protocol population (because of incomplete clinical research document [3 patients], adverse events [2 patients], inability to inhale, and patient requesting discharge because of disappearance of pain). All remaining patients had complete pain intensity records up to and including the 30-minute point. Efficacy results were similar for both the intention-to-treat and per-protocol populations; therefore, only results for the intention-to-treat 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 Table E2 (available online at http://www.annemergmed.com); 2 patients were enrolled in an out-of-hospital emergency unit and all other patients were enrolled in EDs. The majority of patients in the standard analgesic treatment group received treatment with first-step analgesics (mostly intravenous); 126 received nonsteroidal anti-inflammatory drugs (mainly dexketoprofen and ketorolac), 11 received metamizole, and 8 received paracetamol. Five patients received second-step opioid analgesia (intravenous tramadol) and 9 received third-step opioids. One patient was treated with mepivacaine (some patients received more than one drug as standard analgesic treatment). Eighteen patients received intravenous diazepam as a coanalgesic added to the nonsteroidal anti-inflammatory drug, and one patient received diazepam added to intravenous fentanyl.

An adjusted repeated-measures model showed that the mean reduction from baseline in Numeric Rating Scale pain intensity score was significantly larger for the methoxyflurane group than the standard analgesic treatment group at all times, with global reductions during the first 20 minutes of 2.47 versus 1.39 (difference 1.00; 95% confidence interval 0.84 to 1.32) (Table 2 and Figure 2*A*). The reduction in pain intensity was larger for methoxyflurane than standard analgesic treatment regardless of baseline pain intensity (moderate [Numeric Rating Scale score 4 to <7] or severe [Numeric Rating Scale score ≥7]) (Figure 2*B* and *C*) and class of standard analgesic treatment administered (nonopioid or opioids) (Figure 2*D*). Originally, we 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 standard analgesic treatment (including all patients) and baseline pain intensity (independently of the standard analgesic treatment 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 points (Table 3 and Figure E1, available online at http://www.annemergmed.com).

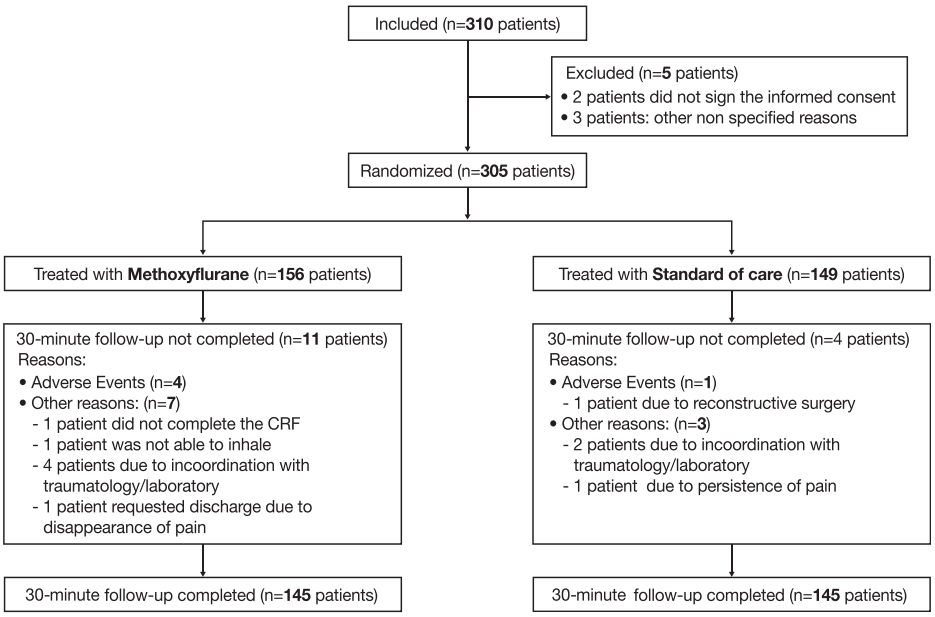

Figure 1. Participant flow. *CRF*, Case report form.

All time-to-event endpoints were significantly shorter (ie, more favorable) for methoxyflurane compared with standard analgesic treatment, including median time to first pain relief (3.17 versus 10.00 minutes [interquartile range {IQR} 1.83 to 7.44 versus 5.74 to 14.64 minutes]), time to first meaningful pain relief (10.00 versus 20.00 minutes [IQR 5.00 to 16.22 versus 1.03 to 29.25 minutes]) (Figure E2, available online at http://www.annemergmed.com), time to pain relief greater than or equal to 2 points on the Numeric Rating Scale (5.00 versus 15.00 minutes [IQR 3.00 to 10.00 versus 10.00 to 27.50 minutes]), and time to maximum pain relief (20.00 versus 30.00 minutes [IQR 15.00 to 30.00 versus 20.00 to 30.00 minutes]). The mean Numeric Rating Scale pain intensity score was similar for both treatment groups at first pain relief (methoxyflurane 5.31 [SD 1.84]; standard analgesic treatment 5.64 [SD 1.58]) and at first meaningful pain relief (methoxyflurane 3.23 [SD 1.78]; standard analgesic treatment 3.55 [SD 1.54]).

Results for patient-averaged summed pain intensity difference 15 minutes after the start of treatment also showed that methoxyflurane provided significantly greater pain relief than standard analgesic treatment (mean –54.13 versus –26.43 [SD 27.25 versus 25.83]). The proportion of pain responders (patients with ≥30% improvement from baseline in Numeric Rating Scale pain intensity score) was significantly higher in the methoxyflurane group than the standard analgesic treatment group (87.9% versus 57.7%). Similarly, the proportion of patients achieving a decrease in pain intensity to less than or equal to 3 points on the Numeric Rating Scale was higher in the methoxyflurane group than the standard analgesic treatment group at both 15 minutes (39.7% versus 14.0%) and 30 minutes (62.2% versus 34.9%).

The number of patients who required rescue medication until discharge was low in both treatment groups (13 patients [8.5%] in the methoxyflurane group and 18 [12.1%] in the standard analgesic treatment group). Two patients received opioids as rescue medication in the methoxyflurane group compared with 9 in the standard analgesic treatment group. Eight patients (5.1%) in the methoxyflurane group required a second methoxyflurane inhaler.

Median scores (on a 0-to-10 scale) for patient satisfaction with methoxyflurane treatment were 9.00 (IQR 8.00 to 10.00) for pain control, 9.00 (IQR 9.00 to 10.00) for comfort of treatment, and 9.00 (IQR 8.00 to 10.00) for safety (adverse events), whereas standard analgesic treatment scored 7.75 (IQR 6.00 to 9.00), 8.00 (IQR 6.38 to 9.50), and 9.00 (IQR 7.00 to 10.00), respectively. Similar results were obtained for clinician satisfaction with treatment. Methoxyflurane treatment exceeded patients' expectations in 77% of cases compared with 38% for standard analgesic treatment (Figure 3*A*), whereas clinicians' expectations were exceeded in 72% of cases for methoxyflurane and 19% for standard analgesic treatment. Higher ratings were also achieved for patients' global impression of change in the methoxyflurane group than the standard analgesic treatment group (Figure 3*B*).

Table 1. Demographic and baseline characteristics (safety population).

Characteristic	Methoxyflurane, N=156	SAT, N=149
Age, mean (SD), y	45.2 (18.75)	45.3 (17.95)
>65, No. (%)	33 (21.2)	26 (17.4)
Sex, No. (%)		
Women	80 (51.3)	69 (46.3)
Baseline NRS score 0–10, mean (SD)	7.6 (1.39)	7.5 (1.46)
Pain intensity score ≥7, No. (%)	127 (82.5)	114 (76.5)
Number of injuries, median (IQR)	1 (1.0–2.0)	1 (1.0–2.0)
Injury type, No. (%)		
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, No. (%)		
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, No. (%)	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,* No. (%)		
IV nonopioids	NA	104 (69.8)
Oral nonopioids	NA	16 (10.7)
IM nonopioids	NA	14 (9.4)
IV opioids	NA	12 (8.1)
TM opioids	NA	2 (1.3)
Others	NA	1 (0.7)

SAT, Standard analgesic treatment; *NRS*, Numeric Rating Scale; *IV*, intravenous; *NA*, not applicable; *IM*, intramuscular; *TM*, transmucosal.
*More than one drug could be administered as SAT.

Table 2. Repeated-measures analysis of reduction from baseline in Numeric Rating Scale pain intensity score during 20 minutes after the start of treatment (intention-to-treat population).

Time, Minutes	Adjusted Reduction From Baseline*		
	Methoxyflurane (N=156)	SAT (N=149)	Estimated Treatment Effect (95% CI)
3	1.45	0.89	0.56 (0.30–0.82)
5	1.98	1.17	0.81 (0.51–1.12)
10	2.62	1.33	1.28 (0.82–1.64)
15	2.89	1.45	1.44 (1.07–1.80)
20	3.19	1.89	1.29 (0.91–1.68)
Overall	2.47	1.39	1.00 (0.84–1.32)

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

In the methoxyflurane group, 38 patients (24.4%) reported a total of 48 adverse events (44 considered treatment related), and in the standard analgesic treatment group, 8 patients (5.4%) reported a total of 9 adverse events (4 considered treatment related). The most common adverse events in the methoxyflurane group were dizziness (22 patients), somnolence (5 patients), and nausea (4 patients). Most adverse events (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 standard analgesic treatment group), and the majority resolved on the same day. Treatment-related adverse events are summarized in Table 4. Five patients experienced a total of 6 serious adverse events; all were related to the trauma injury (pain, surgery, and hospitalization) and none were fatal or related to study treatment. Five patients discontinued because of adverse events; this included 4 patients in the methoxyflurane group because of dizziness (2 patients), nausea and vomiting (1 patient), and verbigeration and dizziness (1 patient), and 1 patient in the standard analgesic treatment group because of surgery. Both methoxyflurane and standard analgesic treatment scored highly (median 9 of 10) in response to the patient and clinician satisfaction question "Are you satisfied with the adverse events experienced for the treatment?"

No clinically significant laboratory abnormalities were identified from the baseline (N=302) or follow-up visit (N=188) laboratory safety results (Table E3, available online at http://www.annemergmed.com). There were no significant differences between methoxyflurane and standard analgesic treatment groups when changes in systolic and diastolic blood pressure and pulse rate between baseline and 30 minutes after the start of treatment were evaluated. Mean changes from baseline in the methoxyflurane and standard analgesic treatment groups at 30 minutes were, respectively, –3.7 versus –2.2 mm Hg (SD 11.6 versus 13.8 mm Hg) for systolic blood pressure, –2.3 versus –0.7 mm Hg (SD 8.6 versus 9.3 mm Hg) for diastolic blood pressure, and –2.7 versus –1.8 beats/min (SD 8.6 versus 8.7 beats/min) for pulse rate. Full vital signs

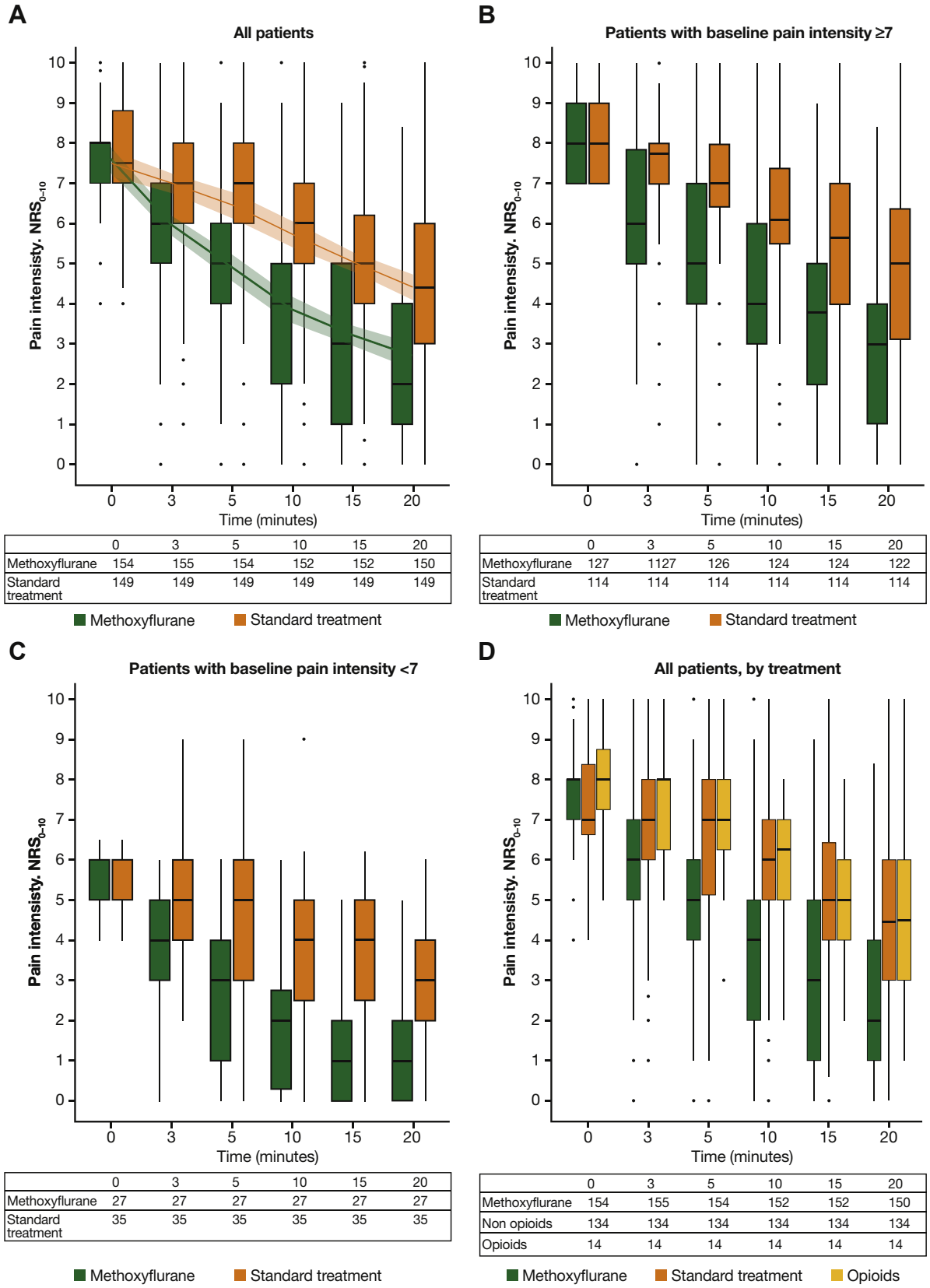

Figure 2. Box plots of Numeric Rating Scale pain intensity score up to 20 minutes (intention-to-treat population).

Table 3. Improvement from baseline in Numeric Rating Scale pain intensity score during 60 minutes after the start of treatment (intention-to-treat population).

Time After Start of Treatment, Minutes	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)

The number of patients with evaluable data=n.

data are provided in Table E4, available online at http://www.annemergmed.com. The Ramsay Sedation Scale score was evaluated before and 30 minutes after the start of treatment. Almost all patients had a score of 2 (cooperative, oriented, and tranquil) at both times; however, in the methoxyflurane arm 3 patients had a score of 1 (anxious, agitated, and restless) before treatment and 1 patient remained at a score of 1 after 30 minutes, and 2 patients had a score of 3 (responsive to commands only) at 30 minutes.

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 standard analgesic treatments (different protocols in each center) and the distinct odor and unique mode of administration of methoxyflurane. Even with a double-blind study design with a single comparator treatment, the dispensing and administration of active and placebo treatments by different routes would potentially delay patient treatment, with ethical implications when rapid analgesia is required. The fact that the mean pain intensity was so similar for both treatment groups at first pain relief (methoxyflurane 5.31 [SD 1.84]; standard analgesic treatment 5.64 [SD 1.58]) and at first meaningful pain relief (methoxyflurane 3.23 [SD 1.78]; standard analgesic treatment 3.55 [SD 1.54]), despite that the time to these pain relief endpoints was 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 of patients (68.5%) in the standard analgesic treatment group received intravenous nonsteroidal anti-inflammatory drugs, there was wide variation in the treatments given as standard analgesic treatment (both oral and intravenous formulations and a range of medication classes, including opioids, benzodiazepines, metamizole, and paracetamol) because of 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 standard analgesic treatment showed that methoxyflurane provided greater pain relief than nonopioid and opioid standard analgesic treatment subgroups. We acknowledge that the differing analgesic protocols in Spain compared with the United States and

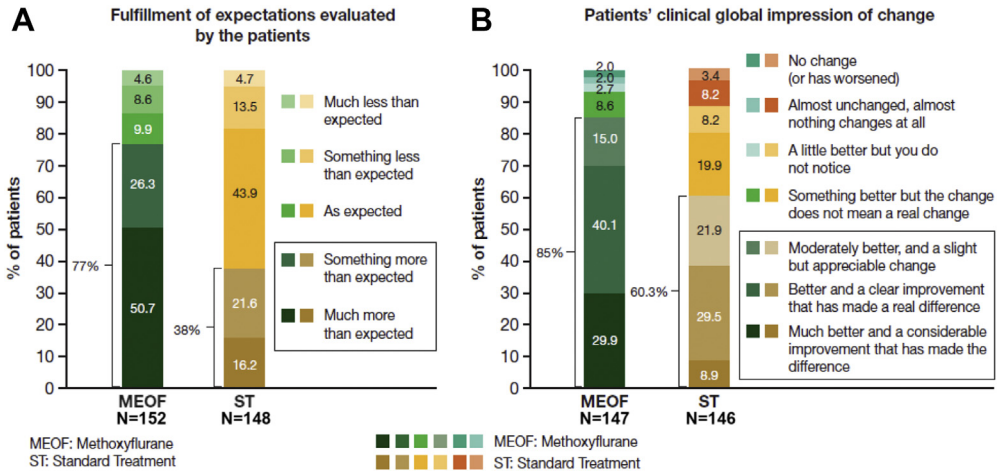

Figure 3. Fulfillment of expectations and clinical global impression of change scored by the patient (intention-to-treat population).

Table 4. Number of patients with treatment-related adverse events (safety population).

	Methoxyflurane (N=156)			SAT (N=149)		
Adverse Event	**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 related; however, no adverse events were reported in this category.

the fact that methoxyflurane is not available in the United States 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 intravenous analgesics (both nonopioids and opioids). The primary endpoint of change in pain intensity during the first 20 minutes after randomization was selected to correspond with the indication of methoxyflurane (ie, emergency relief of moderate to severe pain associated with trauma) and the unmet need for an easy-to-administer, rapid-acting, first-line analgesic treatment in the ED. Given that many of the standard analgesic treatments would not reach peak effect until after 20 minutes, this may have introduced bias in favor of methoxyflurane for the primary endpoint; however, assessments of pain intensity at later times up to 60 minutes after randomization (Table 3) demonstrated favorable results for methoxyflurane versus standard analgesic treatment at all times up to 60 minutes after randomization.

We recognize that the biochemical analysis in this study was constrained by the relatively long interval to the follow-up sample (14 days [SD 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 1 follow-up visit was required in this study, which was set at 14 days (as in the pivotal STOP! study[20,22]) to allow capture of adverse events (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 and 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 hepatotoxicity 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 adverse events,[20-22] although caution is advised when administering it 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, ECGs were not performed. However, a previous phase 1 QT/QTc-interval 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 out-of-hospital 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 with the standard analgesic treatments used in daily practice in 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 randomized controlled trials comparing methoxyflurane with an active comparator. Designing an active-controlled trial in this setting is challenging because of 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 use a pragmatic open-label study design. The most frequently used analgesics in Spanish EDs are nonsteroidal anti-inflammatory drugs (generally administered parenterally), with a relatively low level of opioid use.[33,34] This is reflected in the current study, in which greater than two thirds of patients (68.5%) in the standard analgesic treatment group received intravenous nonsteroidal anti-inflammatory drugs, and only 9.4% received opioid analgesia. Given that nonsteroidal anti-inflammatory drugs are a first-step analgesic,[35] this might be anticipated to lead to more favorable results for methoxyflurane versus standard analgesic treatment than if most patients had received opioid analgesics. However, analysis of the primary endpoint by class of standard analgesic treatment in this study showed a larger mean reduction in pain intensity for methoxyflurane compared with both nonopioid and opioid analgesics (Figure 2*D*). Previous prospective studies have shown methoxyflurane to provide much larger reductions in pain scores than intramuscular tramadol in the emergency setting,[24,25] and although one large retrospective study found similar efficacy of methoxyflurane and intranasal fentanyl,[36] a second showed both intravenous morphine and intranasal fentanyl to 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. An approximately 20% reduction in Numeric Rating Scale pain intensity score corresponds to "minimal improvement" in patients with acute pain,[38] whereas a reduction of greater than or equal to 2 points, or 30%, is the minimum clinically important difference for chronic pain,[39] although the minimum clinically important difference 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 standard analgesic treatment group by 20 minutes. Studies by Todd et al[41] and Gallagher et al[42] suggesting a change of approximately 13 mm on a 100-mm visual analog scale to be the minimum clinically important difference for acute pain provide further support that the improvement in pain intensity with methoxyflurane in this study is clinically relevant to the patient. The finding that mean Numeric Rating Scale pain intensity score was so similar for both treatments at 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 similar to those reported for the STOP! study adult population,[22] although baseline pain intensity in that study was limited to Numeric Rating Scale score less than or equal to 7. The STOP! study demonstrated mean adjusted changes from baseline in visual analog scale pain intensity (0-to-100 scale) of a magnitude similar to the mean adjusted decreases in Numeric Rating Scale pain intensity score in this study. Median time to first pain relief (subjectively assessed by the patient) was 5 minutes in the STOP! study[22] and 3 minutes 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% and 72% of cases, respectively, whereas in the STOP! study adult subgroup, methoxyflurane was rated as excellent, very good, or good by approximately 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 with a range of analgesics, with a fast onset of pain relief within a median of 3 to 5 minutes from the start of treatment. Furthermore, the time required to dispense and administer methoxyflurane is minimal compared with that for parenteral or controlled medications. In this trial, time from randomization to treatment administration was significantly shorter with methoxyflurane than with standard analgesic treatment (median 7.00 versus 10.00 minutes [IQR 4.00 to 11.00 versus 7.00 to 18.25 minutes], respectively). Median duration of ED stay was also shorter for methoxyflurane than standard analgesic treatment (median 107.00 versus 113.50 minutes [IQR 86.75 to 150.00 versus 93.00 to 142.00 minutes], respectively). The methoxyflurane inhaler is easy to use and well accepted by patients and treating health care 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 in regard to emergency use of methoxyflurane were raised in this study. Consistent with the STOP! study[20,22] and the summary of product characteristics,[17] the most frequently occurring adverse event 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 adverse events were transient, resolving the same day, and most were mild. 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 nonsteroidal anti-inflammatory drugs to opioids. However, additional studies versus individual agents are required to fully investigate specific treatment differences. Methoxyflurane may be considered a nonnarcotic, easy-to-administer, rapid-acting, first-line alternative to currently available analgesic treatments for trauma pain.

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Author contributions: All authors conceptualized and contributed to the study design and data collection, and reviewed and revised the article. JCMÁ provided statistical expertise on study design and analyzed the data. AMB supervised study design, patient recruitment, and data collection. All authors approved the final article as submitted and agree to be accountable for all aspects of the work. AMB takes responsibility for the paper as a whole.

All authors attest to meeting the four ICMJE.org authorship criteria: (1) Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND (2) Drafting the work or revising it critically for important intellectual content; AND (3) Final approval of the version to be published; AND (4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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APPENDIX

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