ORIGINAL RESEARCH

Low-Dose Methoxyflurane versus Standard of Care Analgesics for Emergency Trauma Pain: A Systematic Review and Meta-Analysis of Pooled Data

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Purpose: Undertreatment of trauma-related pain is common in the pre-hospital and hospital settings owing to barriers to the use of traditional standard of care analgesics. Low-dose methoxyflurane is an inhaled non-opioid analgesic with a rapid onset of pain relief that is approved for emergency relief of moderate-to-severe trauma-related pain in adults. This analysis was performed to compare the efficacy and safety of low-dose methoxyflurane with standard of care analgesics in adults with trauma-related pain.
Methods: A meta-analysis was performed on pooled data from randomized controlled trials identified via a systematic review. The primary endpoint was the pain intensity difference between baseline and various time intervals (5, 10, 15, 20, and 30 minutes) after initiation of treatment.
Results: The pain intensity difference was statistically superior with low-dose methoxyflurane compared with standard of care analgesics (overall estimated treatment effect=11.88, 95% CI=9.75–14.00; P<0.0001). The superiority of low-dose methoxyflurane was demonstrated at 5 minutes after treatment initiation and was maintained across all timepoints. Significantly more patients treated with methoxyflurane achieved response criteria of pain intensity ≤30 mm on a visual analog scale, and relative reductions in pain intensity of ≥30% and ≥50%, compared with patients who received standard of care analgesics. The median time to pain relief was shorter with methoxyflurane than with standard of care analgesics. The findings were consistent in a subgroup of elderly patients (aged ≥65 years).
Conclusion: Methoxyflurane can be considered as an alternative to standard of care analgesics in pre-hospital and hospital settings for treatment of adult patients with acute trauma-related pain.
Keywords: acute pain, inhaled analgesic, emergency service, wounds and injury, pain management, analgesia

Plain Language Summary

Many patients with trauma injuries do not receive adequate pain relief, which can lead to unnecessary suffering and a prolonged stay in hospital. This may be because their pain-reliving medicine (analgesic) is not effective enough, or because it is difficult to administer (for example if it has to be given through a vein). Low-dose methoxyflurane is an analgesic that patients can administer themselves using an inhaler. It starts working quickly and is effective for around 30 minutes if used continuously. We analyzed the results from four studies in which adults with trauma-related pain were treated with low-dose methoxyflurane or standard analgesics (including paracetamol, anti-inflammatories, and opioids). Our analysis showed that low-dose methoxyflurane provided better and faster pain relief than the standard analgesics. Satisfaction with treatment was higher among patients who received low-dose methoxyflurane than among those who received standard analgesics.

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We repeated the analysis in elderly patients (aged ≥65 years) and got similar results. Based on our findings, we recommend that low-dose methoxyflurane is considered as an alternative to standard analgesics for treatment of trauma-related pain in adults.

Introduction

Despite recommendations that patients with trauma-related pain should receive prompt and effective analgesia during emergency care in both pre-hospital and hospital settings,[1] many patients are undertreated.[1–4] This results in prolonged hospital stays, unnecessary patient suffering, and dissatisfaction.[5–7] A wide range of analgesics is available for use in the pre-hospital and emergency department settings, with a variety of formulations and routes of administration. Healthcare providers can therefore find it challenging to determine the most appropriate treatment.[1] In addition, some commonly-used analgesics are associated with factors that contribute, at least in part, to oligoanalgesia in patients with moderate-to-severe trauma pain.[1,8] These factors include the limited efficacy of weak analgesics, difficulties with intravenous administration, side-effects, the high administrative burden associated with controlled drugs, and logistical constraints (eg, storage of bulky nitrous oxide canisters).

Low-dose methoxyflurane is a non-opioid analgesic that patients self-administer under medical supervision using a hand-held inhaler device. Self-administration allows the patient to titrate the minimum effective dose to relieve their pain, up to a maximum of two 3 mL vials (maximum 15 mL per week). Low-dose methoxyflurane has a number of features that make it an attractive option for analgesia in the pre-hospital and emergency department settings. Onset of pain relief is rapid (within 6–10 inhalations).[9] With continuous use, pain relief lasts for 25–30 minutes; this may be longer with intermittent use.[9] Adverse effects are generally mild and transient, resolving quickly after inhalation is stopped.[9] Low-dose methoxyflurane does not cause respiratory depression and has no effect on cardiovascular function (systolic blood pressure and pulse rate).[10,11] The inhaler is easy to use and allows patients to control their own level of analgesia; it is also compact, making it easy to store.

Low-dose methoxyflurane has been used extensively in Australia for over 40 years to provide short-term relief of acute pain in adults and children.[12–14] It is also available in Canada and South Africa, as well as countries in Asia, Latin America, and the Gulf. In the EU, low-dose methoxyflurane is approved for emergency relief of moderate-to-severe trauma-associated pain in conscious adults.[9] EU approval was granted based on evidence from the randomized, double-blind, placebo-controlled STOP! trial,[15] in which methoxyflurane provided a statistically and clinically significant reduction in pain intensity. Subsequently, low-dose methoxyflurane has been shown to provide superior pain relief to standard of care analgesics in patients with moderate and severe acute trauma pain.[16,17]

To help healthcare providers make informed treatment decisions, comprehensive, high quality analyses of the efficacy and safety data for analgesics used in acute trauma-related pain are needed. The aim of this systematic review and meta-analysis was to compare the analgesic efficacy and safety of low-dose methoxyflurane with that of standard of care analgesics in emergency care of patients with acute trauma-related pain.

Methods

Methods of the meta-analysis and inclusion criteria for the systematic review were specified in advance and documented in a statistical analysis plan.

Systematic Literature Review
Eligibility Criteria

Eligibility criteria were defined using the PICO (population, interventions, comparisons, and outcome) framework. The population of interest was adults receiving emergency care for acute musculoskeletal, trauma-related pain (defined as a visual analogscale [VAS] score ≥4 and lasting for <48 hours, or defined by the study authors as "trauma"). The intervention was low-dose methoxyflurane and the comparator was standard of care (non-steroidal anti-inflammatory drugs [NSAIDs], paracetamol, weak or strong opioids, or no treatment) ± placebo. For studies in which a placebo inhaler was used, standard of care related to the treatments listed above taken before treatment initiation or in the first minute after the first placebo inhalation; for studies in which a placebo was not used, standard of care related to these treatments taken at treatment initiation or in the first minute after treatment initiation. The primary outcome was pain intensity; secondary outcomes were treatment satisfaction and adverse events (AEs). Only prospective randomized clinical trials published in English were eligible for inclusion.

Search Strategies

MEDLINE and Embase were searched up to June 29, 2020 using the search term methoxyflurane AND emergency AND randomi*.

Study Selection and Data Collection

All titles and abstracts identified in the searches were independently screened; eligible abstracts went forward to full text screening and review. Articles that met the eligibility criteria at full text screening were included in the analysis.

Two reviewers independently extracted the following data from the included trials: demographics, exposure, pain intensity scores, time to pain relief, treatment satisfaction, and AEs. Any discrepancies were resolved by referral to a third reviewer.

Meta-Analysis

The primary endpoint of the analysis was the pain intensity difference between baseline and various time intervals (5, 10, 15, 20, and 30 minutes) after initiation of treatment. Secondary endpoints were: relative pain intensity difference; response criteria (level of pain ≤30 mm, relative reduction in pain intensity [RPID] ≥30% and ≥50%); time to pain relief after first inhalation (patient-declared, time to ≥2-point reduction in VAS score and time to VAS score ≤30); treatment satisfaction (assessed by patient, investigator and nurse on a 5-point Likert scale, where 1=very satisfied and 5=very dissatisfied); safety.

The analysis was carried out using individual patient data with a one-step approach as the primary estimate. The pain intensity difference was compared between low-dose methoxyflurane and standard of care analgesics using a repeated measures analysis of variance (ANOVA) model including the study (as a random effect), treatment, nominal time point, and the interaction between treatment and nominal time point. For the primary endpoint, a two-step approach was also used to estimate heterogeneity between the studies and consolidate results: each study data set was analyzed separately using repeated measures ANOVA and the treatment effects across studies were combined using the weighted average of treatment effects (where weights correspond to the inverse of treatment effect variance) with a random effects model (as it is assumed that intervention effects follow a distribution across studies).

Study Populations

Efficacy analyses were carried out on the meta-analysis population (MAP1), which included all patients aged ≥18 years who were randomized to low-dose methoxyflurane or standard of care analgesics ± placebo (patients receiving methoxyflurane plus standard of care analgesics were excluded from the analysis). Safety analyses were carried out on the safety population, ie, all MAP1 patients who received at least one dose of study medication.

Risk of Bias Across Studies

Most studies reported pain intensity on a 100 mm VAS, where 0=no pain and 100=worst pain imaginable. One study used an 11-point numerical rating scale (NRS) (where 0=no pain and 10=unbearable pain);[16] pain intensity data from this study were multiplied by 10 to allow comparison with the other studies. In addition, this study did not report NRS scores at randomization so the score at T_0 (ie, just before the first dose of study medication) was used in place of the score at randomization. To evaluate potential bias regarding use of NRS, a correlation between NRS at randomization and the closest value in the VAS was carried out.

Additional Analysis

All analyses were also carried out in a subpopulation of elderly patients (aged ≥65 years). A sensitivity analysis was carried out that considered standard of care as analgesics taken before treatment initiation or in the first 20 minutes after treatment initiation. The results of this sensitivity analysis are not reported here.

Results

Study Selection

The systematic literature review yielded 56 articles. After initial screening, 23 went forward for full text review. Eighteen of these were excluded; the most common reasons for exclusion were that the studies reported were retrospective or were not randomized controlled trials. The analysis therefore included five publications describing four RCTs: STOP!,[15,19] InMEDIATE,[16] MEDITA,[17] and PenASAP.[18] A flowchart of study identification and selection is shown in Figure 1.

STOP! (NCT01420159) was a randomized, double-blind, multicenter study comparing low-dose methoxyflurane with placebo in patients who presented at UK emergency departments with acute minor trauma.[15,19] The primary outcome of the study was change in pain intensity from baseline to 5, 10, 15, and 20 minutes after first inhalation. The study included 300 patients, 90 of whom were adolescents and therefore outside the scope of this meta-analysis.[15] A subgroup analysis of 204 adult patients included in STOP! has been published.[19]
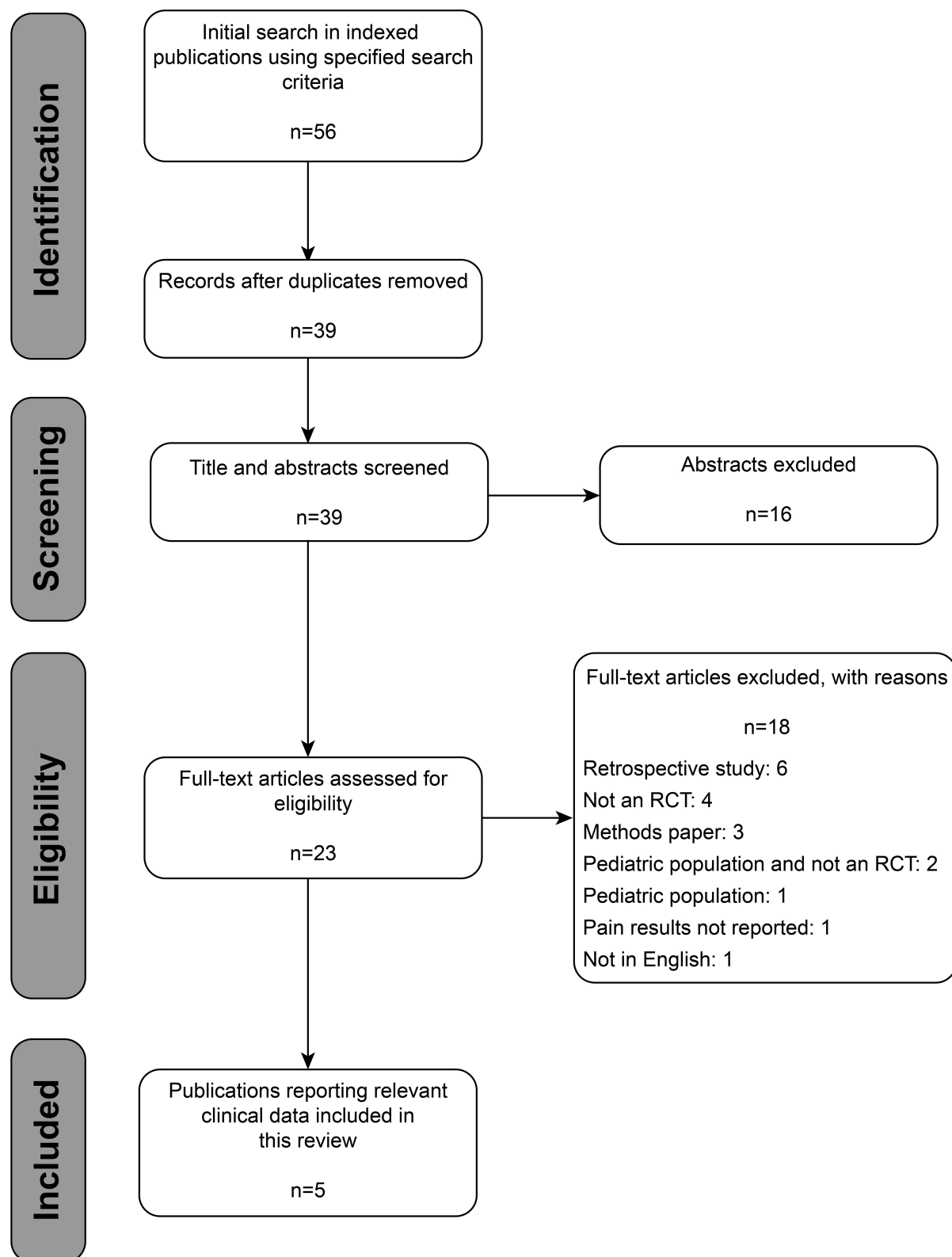
Figure 1 PRISMA flow diagram for study selection.
Abbreviation: RCT, randomized controlled trial.

The randomized open-label InMEDIATE study (NCT03256903) compared low-dose methoxyflurane with standard of care in patients with mild-to-severe trauma pain in Spanish prehospital and emergency department settings.[16] The study had coprimary endpoints of change from baseline in pain intensity during the first 20 minutes of treatment and time to first pain relief. MEDITA (NCT03585374) was a randomized open-label study comparing methoxyflurane and standard of care for moderate-to-severe acute trauma pain in Italian prehospital and emergency department settings.[17] The primary outcome was change in pain intensity from baseline at 3, 5, and 10 minutes after initiation of treatment. The PenASAP study (NCT03798899) was a randomized, double-blind study comparing methoxyflurane (plus standard of care) with placebo (plus standard of care) in patients presenting to the French emergency department with moderate-to-severe trauma-related pain.[18] The primary outcome was time to pain relief. A summary of the key outcomes from these studies is given in Table 1.

Table 1 Key Outcomes from the Included Studies

Study	Interventions	Primary Endpoint	Other Key Endpoints	AEs (% of Patients)
STOP! (adult subgroup analysis)[19]	Methoxyflurane (n=103) Placebo (n=101)	Change in pain intensity from baseline at 5, 10, 15, and 20 minutes (100 mm VAS). Primary analysis: estimated overall treatment effect considering all four timepoints: −17.4 mm (95% CI=−22.3, −12.5); *P*<0.0001	Median time to first pain relief: Methoxyflurane 5 minutes (95% CI=NC); Placebo 20 minutes (95% CI=10.0, NC); HR 2.32 (95% CI=1.63, 3.30); P<0.0001 Treatment satisfaction: Global medication performance rated as excellent, very good, or good by 77.6% of patients in the methoxyflurane group	Methoxyflurane: 62.7% Placebo: 40.6%
InMEDIATE[16]	Methoxyflurane (n=156) SoC[a] (n=149)	Change in pain intensity from baseline during first 20 minutes (1–10 NRS): Methoxyflurane −2.47; SoC −1.32; difference: 1.00 (95% CI=0.84, 1.32) Median time to first pain relief: Methoxyflurane 3 minutes (IQR=1.83–7.44); SoC: 10 minutes (IQR=5.74–14.64)	Proportion of patients with ≥30% improvement in pain intensity: Methoxyflurane 87.9%; SoC 57.7% Treatment satisfaction: Exceeded patient expectation of treatment in 77% of methoxyflurane cases vs 38% of SoC cases	Methoxyflurane: 24.4% SoC: 5.4%
MEDITA[17]	Methoxyflurane (n=135) SoC[b] (n=135)	Change in pain intensity from baseline at 3, 5, and 10 minutes (100 mm VAS) Primary analysis: estimated overall treatment effect considering all three timepoints: −5.94 mm (95% CI=−8.83, −3.06); *P*<0.05	Median time to onset of pain relief: Methoxyflurane: 9 minutes (95% CI=7.72, 10.28); SoC: 15 minutes (95% CI=14.17, 15.83) Treatment satisfaction: Overall efficacy rated excellent, very good, or good by 72.7% of methoxyflurane patients vs 60.9% of SoC patients; *P*=0.001	Methoxyflurane: 17.0% SoC: 3.0%
PenASAP[18]	Methoxyflurane + SoC[c] (m-SoC; n=178) Placebo + SoC (p-SoC; n=173)	Median time to pain relief (VAS ≤30 mm): m-SoC: 35 min (95% CI=28, 62); SoC: not reached (95% CI=92, not reached); HR 1.93 (95% CI=1.43, 2.60); *P*<0.001	Overall pain intensity difference: 9.2 (95% CI=5.3, 13.1); *P*<0.0001 Proportion of patients with ≥30% improvement in pain intensity at 30 minutes: m-SoC 65.5%; p-SoC 45.9%; *P*<0.001 Treatment satisfaction: Global performance rated as excellent, very good, or good by 79% of m-SoC patients vs 54% of p-SoC patients; *P*<0.001	m-SoC: 49% p-SoC: 12%

Notes: [a]SoC in InMEDIATE included NSAIDs, metamizole, paracetamol, IV tramadol, and strong opioids; doses are not reported. [b]SoC defined in MEDITA as IV morphine 0.1 mg/kg for severe pain and IV paracetamol 1 g or IV ketoprofen 100 mg for moderate pain. [c]SoC in PenASAP included non-opioids, weak opioids, and strong opioids; the mean quantity of opioids taken was 4.8 mg morphine equivalent (range=1–15.9 mg) in the m-SoC group and 4.1 mg morphine equivalent (range=0.4–8 mg) in the p-SoC group.
Abbreviations: AE, adverse event; CI, confidence interval; HR, hazard ratio; IQR, interquartile range; IV, intravenous; m-SoC, methoxyflurane plus standard of care; NC, not calculable; NRS, numerical rating scale; NSAIDs, non-steroidal anti-inflammatory drugs; p-SoC, placebo plus standard of care; SoC, standard of care; VAS visual analogscale.

Patients

In total, the four studies included 1,260 patients. Of these, 1,090 were included in MAP1 and 1,102 were included in the safety population. The most common reasons for exclusion from MAP1 were for being a pediatric patient and for being randomized to methoxyflurane but receiving standard of care before or in the first minute after inhalation. Twenty-four patients were excluded from MAP1 because they had VAS scores <30 mm at T_0; these patients were included in the safety population. Overall, 96 pediatric patients were excluded from MAP1; all these patients were in the STOP! study. Table 2 shows patient disposition in the MAP1 and safety populations by treatment group.

Of the 1,090 patients in MAP1, 536 had received low-dose methoxyflurane and 554 had received standard of care ± placebo. Patient demographics were similar between the two groups (Table 3). The mean (SD) age was 43.3 (17.9) years in the methoxyflurane group and 42.2 (18.0) years in the standard of care group. In both treatment groups, most primary injuries were to the lower limb; contusions were the most common type of primary injury (Table 3). Most patients who used either a methoxyflurane or placebo inhaler in the studies needed just one inhaler: 81% of the 536 patients who used a methoxyflurane inhaler and 68% of the 272 who used a placebo inhaler.

Eighty-two patients (15.3%) in the methoxyflurane group and 72 (13.0%) in the standard of care group were aged ≥65 years; patient demographics and disposition for this elderly subgroup population are shown in the Supplementary Table 1.

Meta-Analysis Results

Figure 2 shows the analysis of pain intensity difference. The overall estimated treatment effect was statistically significant and in favor of low-dose methoxyflurane versus pooled standard of care analgesics ± placebo (estimated treatment effect=11.88, 95% CI=9.75–14.00; P<0.0001). The superiority of low-dose methoxyflurane was demonstrated at 5 minutes after treatment initiation and was maintained across all timepoints. A similar pattern was seen when low-dose methoxyflurane was compared with each individual standard of care treatment category; the only instance when methoxyflurane did not show statistical superiority was in the comparison with opioids at T_{30}, although the treatment difference remained in favor of methoxyflurane.

The results for pain intensity difference were similar in the elderly subgroup. The estimated overall treatment effect (95% CI) for methoxyflurane versus pooled standard of care analgesics ± placebo was 8.61 (3.27–13.95); P=0.0016. As in the overall population, superiority of

Table 2 Patient Disposition (MAP1 and Safety Populations)

Population	Not Randomized (N=21)	Methoxyflurane (N=626)	Standard of Care ± Placebo					Total (N=1,260)
			No Treatment (N=313)	Paracetamol (N=117)	NSAID (N=127)	Opioid (N=56)	All (N=613)	
MAP1								
n	21	626	313	117	127	56	613	1260
Included, n (%)	0 (0.0)	536 (85.6)	256 (81.1)	115 (98.3)	127 (100%)	56 (100.0)	554 (90.4)	1,090 (86.5)
Excluded, n (%)	21 (100.0)	90 (14.4)	57 (18.2)	2 (1.7%)	0 (0.0)	0 (0.0)	59 (9.6)	170 (13.5)
Received SoC within 1 minute of inhaling methoxyflurane	0 (0.0)	29 (32.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	29 (17.1)
Aged <18 years	0 (0.0)	48 (53.3)	48 (84.2)	0 (0.0)	0 (0.0)	0 (0.0)	48 (81.4)	96 (56.6)
Not randomized	21 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	21 (12.4)
VAS <30 at T_0	0 (0.0)	13 (14.4)	9 (15.8)	2 (100.0)	0 (0.0)	0 (0.0)	11 (18.6)	24 (14.1)
Safety								
n	0	549	265	117	127	56	565	1114
Included, n (%)	0 (0.0)	543 (98.9)	259 (97.7)	117 (100.0)	127 (100.0)	56 (100.0)	559 (98.9)	1,102 (98.9)
Excluded, n (%)	0 (0.0)	6 (1.1)	6 (2.3)	0 (0.0)	0 (0.0)	0 (0.0)	6 (1.1)	12 (1.1)
Not treated	0 (0.0)	6 (100.0)	6 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (100.0)	12 (100.0)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; SoC, standard of care; T_0, time of treatment initiation; VAS, visual analog scale.

Table 3 Patient Demographics (MAPI)

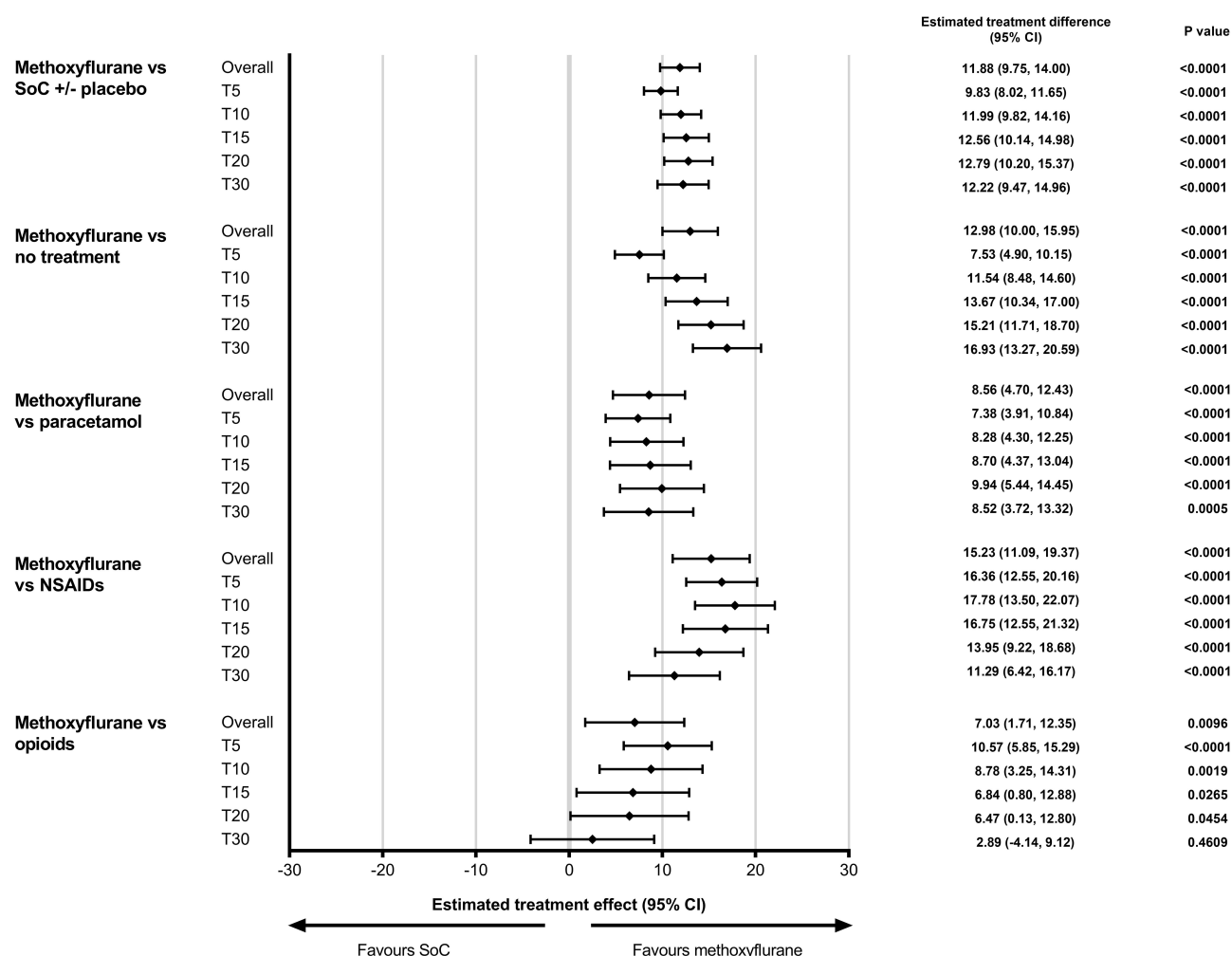|	Methoxyflurane (N=536)	Standard of Care ± Placebo					Total (N=1090)
		No Treatment (N=256)	Paracetamol (N=115)	NSAID (N=127)	Opioid (N=56)	All (N=554)	
Age, years							
Mean (SD)	43.3 (17.9)	36.7 (15.4)	45.2 (18.3)	44.0 (17.6)	56.8 (19.1)	42.2 (18.0)	42.7 (17.9)
Range	18.0–96.3	18.0–84.0	17.9–95.2	18.0–86.0	19.1–95.1	17.9–95.2	17.9–96.3
Age ranges, n (%)							
<65 years	454 (84.7)	240 (93.8)	98 (85.2)	107 (84.3)	37 (66.1)	482 (87.0)	936 (85.9)
≥65 years	82 (15.3)	16 (6.3)	17 (14.8)	20 (15.7%)	19 (33.9)	72 (13.0)	154 (14.1)
Sex, n (%)							
Female	248 (46.3)	115 (44.9)	54 (47.0)	54 (42.5)	38 (67.9)	261 (47.1)	509 (46.7)
Male	288 (53.7)	141 (55.1)	61 (53.0)	73 (57.5)	18 (32.1)	293 (52.9)	581 (53.3)
VAS score at randomization, mean (SD)	67.6 (15.5)	65.0 (13.5)	59.5 (13.7)	73.9 (15.0)	81.4 (10.3)	67.6 (15.1)	67.6 (15.3)
VAS score at T_0, mean (SD)	69.5 (16.2)	67.4 (15.5)	63.8 (16.1)	74.3 (14.5)	79.1 (13.7)	69.4 (16.0)	69.5 (16.1)
Location of primary injury, n (%)							
n	532	254	114	126	56	550	1,082
Lower limb	237 (44.5)	109 (42.9)	56 (49.1)	57 (45.2)	21 (37.5)	243 (44.2)	480 (44.4)
Upper limb	207 (38.9)	108 (42.5)	50 (43.9)	36 (28.6)	33 (58.9)	227 (41.3)	434 (40.1)
Chest	39 (7.3)	4 (1.6)	4 (3.5)	21 (16.7)	2 (3.6)	31 (5.6)	70 (6.5)
Spine	25 (4.7)	20 (7.9)	3 (2.6)	0 (0.0)	0 (0.0)	23 (4.2)	48 (4.4)
Face	22 (4.1)	10 (3.9)	0 (0.0)	12 (9.5)	0 (0.0)	22 (4.0)	44 (4.1)
Pelvis	2 (0.4)	3 (1.2)	1 (0.9)	0 (0.0)	0 (0.0)	4 (0.7)	6 (0.6)
Type of primary injury, n (%)							
n	534	255	115	127	56	553	1,087
Contusion	198 (37.1)	76 (29.8)	43 (37.4)	68 (53.5)	12 (21.4)	199 (36.0)	397 (36.5)
Fracture	152 (28.5)	57 (22.4)	32 (27.8)	22 (17.3)	35 (62.5)	146 (26.4)	298 (27.4)
Sprain	84 (15.7)	56 (22.0)	4 (3.5)	23 (18.1)	0 (0.0)	83 (15.0)	167 (15.4)
Dislocation	41 (7.7)	11 (4.3)	25 (21.7)	8 (6.3)	6 (10.7)	50 (9.0)	91 (8.4)
Wound	25 (4.7)	32 (12.5)	3 (2.6)	2 (1.6)	0 (0.0)	37 (6.7)	62 (5.7)
Other	21 (3.9)	10 (3.9)	7 (6.1)	4 (3.1)	1 (1.8)	22 (4.0)	43 (4.0)
Muscle injury	12 (2.2)	8 (3.1)	1 (0.9)	0 (0.0)	2 (3.6)	11 (2.0)	23 (2.1)
Burn	1 (0.2)	5 (2.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (0.9)	6 (0.6)

Abbreviations: NSAID, non-steroidal anti-inflammatory drug; SD, standard deviation; VAS, visual analog scale.

methoxyflurane was seen at 5 minutes and was maintained at all timepoints.

For RPID, the estimated overall treatment effect (95% CI) for methoxyflurane versus pooled standard of care analgesics ± placebo was 17.43 (14.71– 20.54); $P<0.0001$ in the overall population. In the elderly subgroup, this was 10.57 (3.20–17.94); $P=0.0050$.

Low-dose methoxyflurane was also statistically superior to pooled standard of care analgesics ± placebo in terms of response criteria across all time points (Table 4). By T_{20}, approximately half the patients (51.9%) treated with low-dose methoxyflurane achieved

pain intensity <30 mm (considered a marker for effective pain relief in emergency departments), compared with less than one-third (29.8%) who received standard of care analgesics. Consistent results were seen when low-dose methoxyflurane was compared with each individual standard of care treatment category; the only instances when methoxyflurane did not show statistical superiority were for relative reductions in pain intensity ≥30% and ≥50% compared with opioids at T_{30}, and pain intensity ≤30 mm compared with paracetamol at T_{15} and T_{20}. A similar pattern was seen in the elderly subgroup, although treatment differences were less marked (see

		Estimated treatment difference (95% CI)	P value
Methoxyflurane vs SoC +/- placebo	Overall	11.88 (9.75, 14.00)	<0.0001
	T5	9.83 (8.02, 11.65)	<0.0001
	T10	11.99 (9.82, 14.16)	<0.0001
	T15	12.56 (10.14, 14.98)	<0.0001
	T20	12.79 (10.20, 15.37)	<0.0001
	T30	12.22 (9.47, 14.96)	<0.0001
Methoxyflurane vs no treatment	Overall	12.98 (10.00, 15.95)	<0.0001
	T5	7.53 (4.90, 10.15)	<0.0001
	T10	11.54 (8.48, 14.60)	<0.0001
	T15	13.67 (10.34, 17.00)	<0.0001
	T20	15.21 (11.71, 18.70)	<0.0001
	T30	16.93 (13.27, 20.59)	<0.0001
Methoxyflurane vs paracetamol	Overall	8.56 (4.70, 12.43)	<0.0001
	T5	7.38 (3.91, 10.84)	<0.0001
	T10	8.28 (4.30, 12.25)	<0.0001
	T15	8.70 (4.37, 13.04)	<0.0001
	T20	9.94 (5.44, 14.45)	<0.0001
	T30	8.52 (3.72, 13.32)	0.0005
Methoxyflurane vs NSAIDs	Overall	15.23 (11.09, 19.37)	<0.0001
	T5	16.36 (12.55, 20.16)	<0.0001
	T10	17.78 (13.50, 22.07)	<0.0001
	T15	16.75 (12.55, 21.32)	<0.0001
	T20	13.95 (9.22, 18.68)	<0.0001
	T30	11.29 (6.42, 16.17)	<0.0001
Methoxyflurane vs opioids	Overall	7.03 (1.71, 12.35)	0.0096
	T5	10.57 (5.85, 15.29)	<0.0001
	T10	8.78 (3.25, 14.31)	0.0019
	T15	6.84 (0.80, 12.88)	0.0265
	T20	6.47 (0.13, 12.80)	0.0454
	T30	2.89 (-4.14, 9.12)	0.4609

Estimated treatment effect (95% CI)

← Favours SoC   Favours methoxyflurane →

Figure 2 Pain intensity difference repeated measures ANOVA (MAP1).
Abbreviations: ANOVA, analysis of variance; CI, confidence interval; NSAIDs, non-steroidal anti-inflammatory drugs; SoC, standard of care; T_5, 5 minutes after treatment initiation; T_{10}, 10 minutes after treatment initiation.

Supplementary Table 2; Supplementary Figure 1). By T_{20}, 42.5% of the 82 elderly patients treated with low-dose methoxyflurane achieved pain intensity <30 mm, compared with 28.6% of the 154 who received standard of care analgesics.

Time to pain relief was shorter with low-dose methoxyflurane than with any of the standard of care treatments (Table 5). The median time to patient-declared pain relief was 10 minutes with methoxyflurane vs 18 minutes with pooled standard of care treatments (hazard ratio=2.03; 95% confidence interval=1.75–2.36; P<0.0001). The median time to a ≥30% reduction in pain intensity was 10 minutes with methoxyflurane, compared with 20 minutes with pooled standard of care analgesics (hazard ratio=1.93; 95% confidence interval=1.68–2.23; P<0.0001). Patients in the "no treatment" group had the longest median time

to pain relief: not evaluable for patient declared pain relief and 31 minutes for ≥30% reduction in pain intensity. A similar pattern was seen in the elderly subgroup (see Supplementary Table 3), although the hazard ratios were only statistically significant for methoxyflurane vs NSAIDs (time to patient declared pain relief) and methoxyflurane vs no treatment (time to ≥reduction in pain intensity).

Compared with standard of care analgesics, low-dose methoxyflurane was associated with a higher proportion of patients who were "satisfied" or "very satisfied" with treatment: 63.5% vs 49.2% (Figure 3). A similar pattern of treatment satisfaction was seen among nurses, study investigators, and the subgroup of elderly patients (see Supplementary Table 4; Supplementary Figure 2).

Table 4 Response Criteria (MAPI): Changes in Pain Intensity Over Time

	Methoxyflurane (N=536)	Standard of Care ± Placebo								All (N=554)	P-value[a]
		No Treatment (N=256)	P-value[a]	Paracetamol (N=115)	P-value[a]	NSAID (N=127)	P-value[a]	Opioid (N=56)	P-value[a]		
Pain Intensity ≤30 mm, n (%)											
T_5	104 (19.9) n=523	21 (8.6) n=245	0.0001	10 (9.0) n=111	0.0125	14 (11.1) n=126	0.0202	1 (1.8) n=56	0.0111	46 (8.6) n=538	<0.0001
T_{10}	181 (35.3) n=513	33 (14.2) n=232	<0.0001	22 (19.5) n=113	0.0137	19 (15.2) n=125	<0.0001	4 (7.1) n=56	0.0002	78 (14.4) n=526	<0.0001
T_{15}	218 (43.7) n=499	45 (19.7) n=228	<0.0001	39 (34.2) n=114	0.3343	29 (23.4) n=124	<0.0001	9 (16.1) n=56	0.0004	122 (23.4) n=522	<0.0001
T_{20}	258 (51.9) n=497	58 (25.2) n=230	<0.0001	41 (36.3) n=113	0.0517	42 (33.6) n=125	<0.0001	15 (27.3) n=55	0.0011	156 (29.8) n=523	<0.0001
T_{30}	302 (60.2) n=502	65 (28.3) n=230	<0.0001	52 (47.3) n=110	0.0243	59 (47.2) n=125	<0.0001	21 (44.7) n=47	0.0045	197 (38.5) n=512	<0.0001
Relative reduction ≥30%, n (%)											
T_5	215 (41.1) n=523	40 (16.3) n=245	<0.0001	18 (16.2) n=111	0.0011	24 (19.0) n=126	<0.0001	4 (7.1) n=56	<0.0001	86 (16.0) n=538	<0.0001
T_{10}	301 (58.7) n=513	55 (23.7) n=232	<0.0001	39 (34.5) n=113	0.0004	32 (25.6) n=125	<0.0001	21 (37.5) n=56	0.0014	147 (27.9) n=526	<0.0001
T_{15}	333 (66.7) n=499	81 (35.5) n=228	<0.0001	53 (46.5) n=114	0.0030	52 (41.9) n=124	<0.0001	31 (55.4) n=56	0.0765	217 (41.6) n=522	<0.0001
T_{20}	363 (73.0) n=497	89 (38.7) n=230	<0.0001	58 (51.3) n=113	0.0002	73 (58.4) n=125	<0.0001	35 (63.6) n=55	0.0509	255 (48.8) n=523	<0.0001
T_{30}	379 (75.5) n=502	95 (41.3) n=230	<0.0001	70 (63.6) n=110	0.0126	94 (75.2) n=125	0.0018	37 (78.7) n=47	0.4289	296 (57.8) n=512	<0.0001
Relative reduction ≥50%, n (%)											
T_5	112 (26.7) n=420	13 (6.0) n=218	<0.0001	7 (7.0) n=100	0.0040	10 (8.9) n=112	<0.0001	1 (1.9) n=53	0.0047	31 (6.4) n=483	<0.0001
T_{10}	197 (48.2) n=409	32 (15.3) n=209	<0.0001	14 (15.9) n=88	<0.0001	20 (17.7) n=113	<0.0001	5 (12.5) n=40	<0.0001	71 (15.8) n=450	<0.0001
T_{15}	235 (58.6) n=401	44 (23.0) n=191	<0.0001	30 (33.0) n=91	0.0028	36 (33.3) n=108	<0.0001	14 (35.9) n=39	0.0062	124 (28.9) n=429	<0.0001
T_{20}	276 (67.3) n=410	56 (28.4) n=197	<0.0001	32 (36.8) n=87	<0.0001	47 (47.5) n=99	<0.0001	23 (53.5) n=43	0.0189	158 (37.1) n=426	<0.0001
T_{30}	328 (72.7) n=451	65 (32.5) n=200	<0.0001	51 (56.0) n=91	0.0037	67 (68.4) n=98	0.0002	30 (75.0) n=40	0.3148	213 (49.7) n=429	<0.0001

Note: [a]P-value vs methoxyflurane.
Abbreviations: T_5, 5 minutes after administration; T_{10}, 10 minutes after administration.

Table 5 Time to Pain Relief (MAPI)

| | Methoxyflurane (N=536) | Standard of Care ± Placebo | | | | |
		No Treatment (N=256)	Paracetamol (N=115)	NSAID (N=127)	Opioid (N=56)	All (N=554)
Patient-declared time to pain relief						
Median (95% CI), minutes	10 (8, 10)	NE (44, NE)	19 (15, 30)	11 (10, 12)	12 (10, 15)	18 (15, 20)
HR (95% CI) vs methoxyflurane	–	0.40 (0.31, 0.52)	0.62 (0.47, 0.81)	0.44 (0.35, 0.56)	0.71 (0.52, 0.97)	2.03 (1.75, 2.36)
P-value	–	<0.0001	0.0006	<0.0001	0.0313	<0.0001
Time to ≥30% reduction in pain						
Median (95% CI), minutes	10 (NE, NE)	31 (27, NE)	20 (15, 25)	20 (15, 30)	15 (12, 20)	20 (20, 28)
HR (95% CI) vs methoxyflurane	–	0.48 (0.38, 0.60)	0.60 (0.47, 0.78)	0.45 (0.35, 0.58)	0.66 (0.48, 0.90)	1.93 (1.68, 2.23)
P-value	–	<0.0001	<0.0001	<0.0001	0.0096	<0.0001

Abbreviations: CI, confidence interval; HR, hazard ratio; NE, not evaluable; NSAID, non-steroidal anti-inflammatory drug.

The incidence of AEs was low and generally comparable between methoxyflurane and standard of care analgesics. However, low-dose methoxyflurane was associated with a higher incidence of dizziness (16.7% vs 3.6%), somnolence (5.9% vs 0.9%), and feeling drunk (4.0% vs 0.5%) than standard of care analgesics. Serious and severe (ie, Grade 3 or 4) AEs were reported by less than 1% of patients, regardless of whether they received methoxyflurane or standard of care analgesics. The safety profile in the elderly population reflected that observed in the overall population.

Discussion

This meta-analysis based on four randomized clinical trials showed that low-dose methoxyflurane provided superior efficacy to a range of standard of care analgesics when used for emergency care of adults with acute musculoskeletal, trauma-related pain. The analysis confirmed the fast onset of pain relief with low-dose methoxyflurane: superior analgesia was demonstrated in the primary endpoint (pain intensity difference) from 5 minutes post-initiation and was maintained throughout the 30-minute assessment period. The superior analgesic effect of low-dose methoxyflurane was consistent across a range of other endpoints, including time to pain relief and various response criteria. The improvements in pain measures were supported by greater treatment satisfaction with low-dose methoxyflurane compared with standard of care analgesics, as reported by patients, nurses, and study investigators. All the analgesics included in the analysis were well tolerated; mild, transient dizziness and somnolence were more frequent with low-dose methoxyflurane than with standard of care analgesics, which is consistent with its known safety profile.

There was no evidence that the efficacy or safety of low-dose methoxyflurane differs in elderly patients: outcomes in patients aged ≥65 years were comparable with the overall population. Some caution is needed when interpreting data in the elderly subgroup given the low patient numbers (82 in the methoxyflurane group and 72 in the standard of care group). Nevertheless, we consider the data to be sufficiently robust as the calculated a posteriori power was 80% for the elderly subgroup.

To our knowledge, this is the first review of pooled data comparing low-dose methoxyflurane with a range of standard of care analgesics used to manage acute trauma-related pain. Coupled with additional benefits that methoxyflurane has over other short-acting analgesics such as
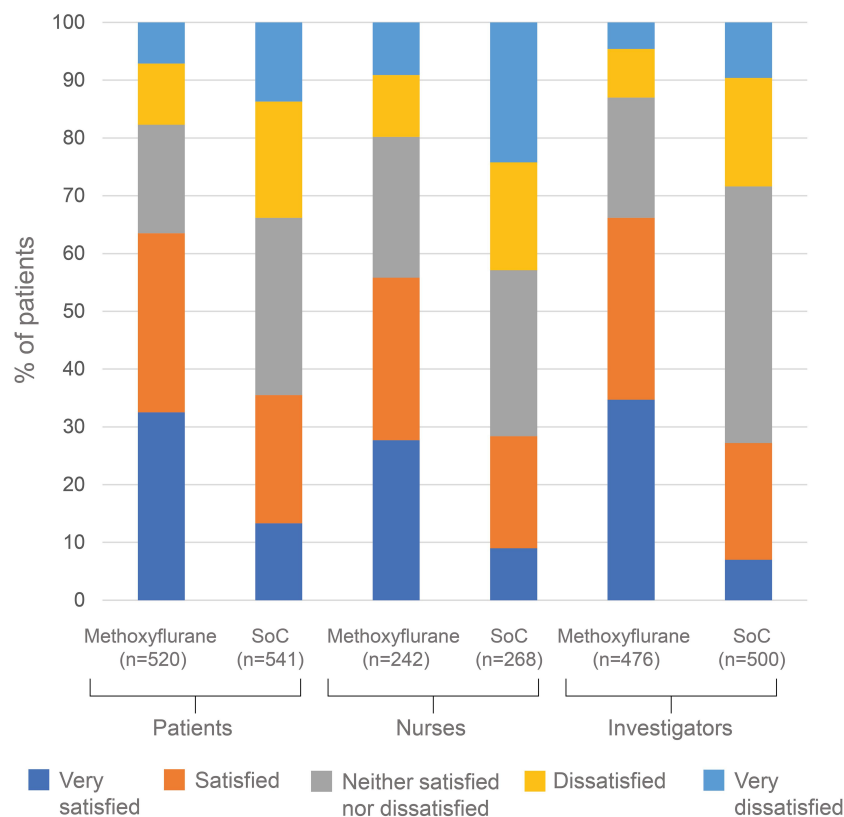
Figure 3 Treatment satisfaction.
Abbreviation: SoC, standard of care.

ease of use, a non-opioid mechanism of action, and the ability for patients to self-titrate to pain control, this meta-analysis provides reassurance to healthcare providers that low-dose methoxyflurane is also a highly effective short-term treatment option in this setting.

It is important that patients are carefully coached in use of the inhaler. Methoxyflurane is added to the inhaler via a one-way valve and absorbed by a polypropylene wick. Once absorbed, methoxyflurane vaporizes and the patient can inhale the vapor through the mouthpiece. Patients should be told to take gentle breaths at first, and then to inhale intermittently to achieve adequate analgesia. As patients exhale into the inhaler, any exhaled methoxyflur-ane is captured in an activated carbon chamber, which reduces the risk of exposure. Non-interventional and observational studies show that occupational exposure to methoxyflurane among healthcare providers who are supervising patients using the inhaler is very low.[20,21]

This meta-analysis only included data from adults with acute trauma pain. This is a limitation but is in line with the current EU approval for methoxyflurane. A recent systematic review found no evidence that the efficacy, onset of action, or safety of low-dose methoxyflurane differ between adults and children.[22]

Another limitation is that the included studies were limited to hospital emergency departments in the UK, France, Italy, and Spain; however, the standard of care analgesics included in the analysis broadly reflect treatments that are commonly used in other countries for pain relief in patients with musculoskeletal trauma injuries.[23] Our literature review did not identify any randomized controlled trials in the pre-hospital setting.

Although the mean age was similar between the methoxyflurane and overall standard of care groups (43.3 years vs 42.2 years, respectively), patients who received opioids were older (56.8 years). These patients also had more severe pain at randomization than patients receiving methoxyflurane or any of the other standard of care treatments. However, this should be interpreted with caution given the low number of patients who received opioids (n=56).

Further limitations include differences in the study designs (ie, some were double-blind and others were

open label) and in the way pain scores were captured (eg, via tablet, on paper, or using a sliding scale ruler).

Conclusion

Low-dose methoxyflurane provides superior and more rapid pain relief to standard of care analgesics commonly used in the pre-hospital and emergency room settings. It should therefore be considered in these settings for treatment of adult patients with acute trauma-related pain.

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