ORIGINAL RESEARCH

Does Inhaled Methoxyflurane Implement Fast and Efficient Pain Management in Trauma Patients? A Systematic Review and Meta-Analysis

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ABSTRACT

Introduction: Evidence on the use of inhaled methoxyflurane in the management of trauma pain is conflicting and obfuscated. This study aimed to determine the efficacy and safety of inhaled methoxyflurane for trauma pain on the basis of published randomized controlled trials (RCTs).

Methods: RCTs assessing the efficacy of methoxyflurane in adults or adolescents with acute trauma pain published in PubMed, Web of Science, Embase, Cochrane Library, and

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40122-021-00258-9.

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Google Scholar were searched. The control groups were those that received placebo or standard analgesic treatment (SAT). The primary outcome was the change from baseline in pain scores during the first 30 min of treatment. Secondary outcomes included time to first pain relief, the proportion of patients experiencing pain relief, rescue analgesia rate, the treatment satisfaction of patients and investigators, and the methoxyflurane-related treatment-emergent adverse events (TEAEs).

Results: A total of nine RCTs (1806 patients) were identified. Results revealed that methoxyflurane provided a clinically unimportant benefit by improving the mean difference of change from baseline in pain intensity (from − 0.44 to − 1.23 cm, $p < 0.001$) at various time points within the first 20 min compared to control treatment. Besides, methoxyflurane decreased the time of onset of pain relief (mean difference − 5.29 min; 95% CI − 6.97 to − 3.62) and the proportion of patients who needed rescue analgesic medication (risk ratio 1.41; 95% CI 1.17–1.70) despite it increasing the risk of non-severe TEAEs (risk ratio 3.09; 95% CI 1.72–5.57). Notably, the benefit of almost all secondary pain-related outcomes was rendered clinically nonsignificant between methoxyflurane and SAT strata besides the time of onset of pain relief. The quality of evidence was low or very low in all outcomes.

Conclusions: In emergency situations without effective therapy, this systematic review and meta-analysis provides low-quality evidence that

methoxyflurane can be used as a rapid-acting and effective treatment for acute trauma pain, although its utilization is associated a risk of non-severe TEAEs. However, the current evidence does not support the notion that inhaled methoxyflurane offered superior analgesic efficacy to SAT.
Clinical Trial Number: PROSPERO registration number CRD42020223000.

Keywords: Methoxyflurane; Trauma pain; Systematic review; Meta-analysis

Key Summary Points

Why carry out this study?

Several previously published reviews examining the effect of methoxyflurane have suggested benefit in emergency department patients, but definitive conclusions are limited by imprecision and non-quantitative analysis.

In addition, the results of methoxyflurane-related adverse reactions in trauma patients are controversial, with conflicting trial results. With the recent publication of several high-quality trials, a specific pooled effect analysis aiming to evaluate the real effect of methoxyflurane was necessary.

What was learned from the study?

This meta-analysis was aimed at evaluating the efficacy and safety of inhaled methoxyflurane for trauma pain during emergency procedures.

The meta-analytic results provided low-quality evidence that methoxyflurane may be considered a simple, rapid-acting, and effective therapeutic option for acute trauma pain, despite the higher incidence of non-severe treatment-emergent adverse events.

Compared to standard analgesic treatment, superiority of the analgesic advantage of methoxyflurane was not particularly pronounced. This finding is attributable to the drug onset time.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14216249.

INTRODUCTION

In hospital emergency departments (EDs), pain is one of the most common complaints presented by patients [1]. However, pain management in pre-hospital settings or in the ED is unsatisfactory [2, 3]. Studies have documented that effective trauma pain management is very important for enhancing patient therapeutic compliance, quality of life, and satisfactory outcomes, which leads to shorter hospital stays [4, 5]. Traditional pharmacotherapeutic options for acute pain in trauma settings include different kinds of opioid and non-opioid drugs (e.g., morphine, nitrous oxide, non-steroidal anti-inflammatory drugs) [6–8]. However, evidence suggests that these drugs confer an increased likelihood of bleeding, mood disorders, and death in trauma patients [9–11]. Thus, access to an effective therapeutic option with less severe adverse reactions is urgently required.

Methoxyflurane is a highly volatile halogenated ether that is administered through a portable inhaler [12]. Recently, the value of methoxyflurane at subanesthetic concentrations has continued to attract a lot of attention owing to its rapid analgesia and without significant nephrotoxicity [13–21]. On the basis of the results of the STOP! phase III trial [16], which demonstrated that methoxyflurane is effective and well tolerated in the management of acute trauma pain with a rapid onset of analgesia, it has been recommended by the European Society for Emergency Medicine as an emergency reliever of moderate-to-severe trauma pain in conscious adults [22]. In Australasia, methoxyflurane is also licensed for the management of trauma pain in adults and children [23].

Several previously published reviews examining the effect of methoxyflurane have suggested benefit in ED patients, but definitive conclusions are limited by imprecision and non-quantitative analysis [24–26]. A recently published article only summarized the completed or ongoing main studies in Europe without performing a systematic literature review [24]. In addition, the results of methoxyflurane-related adverse reactions in trauma patients are controversial, with conflicting trial results [13, 14, 20, 21]. With the recent publication of several high-quality trials, a specific pooled effect analysis aiming to evaluate the real effect of methoxyflurane is necessary.

Therefore, we performed this meta-analysis of randomized controlled trials (RCTs) to evaluate the efficacy and safety of inhaled methoxyflurane for trauma pain. The change in pain intensity score at various time points within 30 min after the start of treatment was designated as the primary outcome. We also assessed the potential efficacy of methoxyflurane in patients of different age (adolescents vs adults) and the intervention of the control group (normal saline inhaled vs standard analgesic treatment, SAT) by a predefined subgroup analysis. Finally, we conducted a comprehensive evaluation of adverse drug reactions with the aim of gaining greater insights into the safety of methoxyflurane.

METHODS

Search Strategy

On the basis of the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and recommendations from the Cochrane Collaboration [27], a systematic search was performed in PubMed, Web of Science, Embase, and the Cochrane Central Register of Controlled Trials. Additionally, Google Scholar was used to retrieve gray literature. On December 27, 2020, this meta-analysis was registered on PROSPERO (CRD42020223000). We last updated our search on January 5, 2021 to ensure that there were no

new trials that would meet the inclusion criteria for our study.

The search strategy was developed with the assistance of an information specialist. Keywords and free-text words associated with methoxyflurane, trauma pain, emergency department, pre-hospital, as well as the sensitive search strategy filter developed by Cochrane were used to identify RCTs. The full search strategy is shown in the supplementary material (eMethods 1–5). Furthermore, we searched ClinicalTrials.gov and the International Clinical Trial Registry Platform for completed and ongoing trials. A manual search was also performed in the reference lists of included studies and similar articles. Finally, we searched the Web of Science and EMBASE for conference proceedings.

Eligibility Criteria and Study Selection

We included RCTs if they involved patients with trauma pain who were randomized to methoxyflurane inhalation and compared to placebo or SAT; involved adolescents (at least 12 years of age) and adult patients with any type of trauma and who received methoxyflurane inhalation at any dose; and if they reported at least one of the following outcomes: change in pain scores at multiple time points, treatment-associated adverse events, number of pain relief, or time of pain relief. Conference papers were included if we could extract accurate data that did not overlap with published studies. Studies that only presented protocols or did not have complete data were excluded. There were no language restrictions.

Two reviewers (HL and XF) independently screened the titles and abstracts. Full texts were subsequently reviewed for all potentially relevant studies. Any discrepancies were adjudicated by two other reviewers (YFR and LJL).

Data Extraction

Two authors (SYT and SRX) independently extracted the data using a standardized data extraction form. The extracted information included the name of the main author, the year

of publication, the type of surgery, sample size, details of the intervention and control, and outcomes. Study authors were contacted for clarifications in case the population characteristics, follow-up method, or outcome data were unclear or not reported.

Assessment of Methodology Quality and Risk of Bias

Methodological quality of the included RCTs was independently reviewed by two reviewers (HL and XF). The Cochrane Collaboration's risk of bias tool was used [28]. The quality of each article was evaluated using seven domains (random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias). In case of disagreements, two reviewers (YFR and WS) discussed to reach a consensus. If one or more domains were found to be high, the overall assessment of the study would be considered as high risk of bias. A risk-of-bias summary table was created in Review Manager, version 5.3. Additional details are included in the supplementary material (eTable 1, eFig. 1A, B).

Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Profiler 3.6 software was used to evaluate the evidence quality for each outcome, which was classified as high ($\oplus\oplus\oplus\oplus$), moderate ($\oplus\oplus\oplus\bigcirc$), low ($\oplus\oplus\bigcirc\bigcirc$), or very low ($\oplus\bigcirc\bigcirc\bigcirc$) [29, 30]. Assessments included risk of bias, inconsistency, indirectness, imprecision, and other considerations [29, 30]. Determination of evidence quality was performed by two independent reviewers (HL and XF) and any disagreements were resolved by consensus with other reviewers (WS and LJL).

Measurement of Primary and Secondary Outcomes

The primary outcome of this meta-analysis was the change in pain intensity score at 3, 5, 10, 15, 20, 25, and 30 min after the start of treatment. There were two types of pain score definitions:

visual analogue scale (VAS) that ranged from 0 to 100, 0 corresponding to no pain and 100 representing the worst imaginable pain; numeric rating scale (NRS) that ranged from 0 to 10, 0 = no pain and 10 = unbearable pain. Pain intensities of all included studies were presented as a 10-point scale (0, no pain; 10, worst pain) by simple transformations [31, 32].

Secondary pain-related outcomes of this review include the time from the start of treatment to first pain relief (subjectively reported by the patient, in minutes), the proportion of patients experiencing pain relief until their departure from the ED (for definitions of pain relief in different studies, see supplementary material eTable 2), and the proportion of patients administered rescue analgesic medication until they were discharged from the ED.

Other secondary outcomes include the proportion of patients and investigators (physicians or nurse) who assessed the satisfactory factor and rated it as excellent, very good, or good, and the methoxyflurane-related treatment-emergent adverse events (TEAEs). Before ED discharge, satisfaction was measured using a five-point Likert scale (poor, fair, good, very good, excellent) [13]. The comprehensive evaluation indicators of methoxyflurane-related TEAEs were summarized and reported by the total incidence of TEAEs, the most common TEAEs occurring with methoxyflurane (dizziness, somnolence, feeling drunk, and headache), and system organ classes were defined according to the Medical Dictionary for Regulatory Activities [17]. All TEAEs were recorded from enrollment until ED discharge, with any subsequent TEAEs also being recorded at the follow-up visit on 14 ± 2 days.

Statistical Analysis

For all continuous effects, the mean $\pm$ standard deviation (SD) was sought. If continuous variables were not presented as mean and SD, we contacted the corresponding author for the original data. If no response was received from the author, statistical conversions were conducted using the presented data. Specifically, the median and interquartile range were

employed to approximate the mean and SD using the methods described by Wan et al. [33]. In situations where a mean and 95% CI were given, conversions were made to a mean and SD using the methods defined by the Cochrane Collaboration [34]. Moreover, the SD was calculated by multiplying standard error by the square root of the number of patients [35]. Finally, data reported in graphical form were derived using the GetData Graph Digitizer Software (GetData Pty Ltd., Kogarah, Australia).

Meta-Analysis

Review Manager 5.3 (Cochrane Collaboration, Nordic Cochrane Centre, London, UK) was used for statistical analysis. Study weights for continuous variables were generated by the inverse variance method, and the Mantel–Haenszel method for dichotomous variables [36]. A weighted mean difference (WMD) with 99% confidence interval (CI) was used for our primary outcome to decrease the risk of type I error associated with repeated testing, and a threshold for statistical significance (a two-sided p value of < 0.01) adjusted by the Bonferroni–Holm correction was considered statistically significant [37, 38]. A negative mean difference implies that the methoxyflurane group, compared with the control group, had a higher magnitude of decrease in pain score between baseline and follow-up. For the continuous secondary outcome of the time to first pain relief, a WMD and 95% CI was calculated; and for the dichotomous secondary outcomes including the proportion of pain relief, the proportion of rescue analgesic medication, the satisfaction assessment, and the incidence of TEAEs, a risk ratio (RR) with 95% CI was calculated. A two-sided $p < 0.05$ was considered statistically significant.

Interpretation of Outcome Results

For the change in pain intensity score at different time points after the start of treatment, the results were interpreted in light of the minimal clinically important difference in pain scores. This difference has been defined to be a 1.3- to 1.5-cm change at a single time point for ED patients [39, 40]. Although not rigorously established, for the outcome of time from the start of treatment to first pain relief, we used a 4-min difference to interpret the treatment effect [24, 26].

Heterogeneity, Sensitivity, and Subgroup Analysis

I^2 statistics were used to assess the heterogeneity of the included studies. If $I^2 < 50\%$, heterogeneity was considered not significant, and the fixed-effects model was applied; otherwise, we assumed that there was significant heterogeneity and used the random-effects model to calculate the effect size. If $I^2 > 50\%$ was observed, sensitivity and subgroup analyses were performed to explore the sources of heterogeneity [34].

A priori sensitivity analysis was carried out by excluding the studies with a high risk of bias, and a post hoc sensitivity analysis was also conducted by excluding the results of the PenASAP trial [19]. The PenASAP findings were excluded because the procedures used SAT in both experimental and the normal saline groups, had the largest sample size, and declared that companies participated in the trial [19]; of note, this was explained by the authors in their introduction as an effort to investigate specific efficacy and safety data in the elderly population [19]. Additionally, we performed a predefined subgroup analysis based on baseline characteristics, namely age (adolescents vs adults) and the intervention of the control group (normal saline inhaled vs SAT). Notably, we did not perform subgroup analysis of methoxyflurane doses as they were consistent in all included studies, although planned in previous protocol registration. All non-prespecified analysis should be considered as exploratory.

Assessment of Publication Biases

For more than ten trials, a funnel plot is usually used to assess the possibility of publication bias. Although planned, we did not construct funnel

plots to assess the publication bias for all outcomes as these are inaccurate when the number of included trials is less than ten [41, 42].

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

From the 246 studies identified in our search, 93 duplicates were removed. A total of 153 studies had their titles and abstracts screened for eligibility. Of the resultant 153 citations, 119 were excluded on the basis of title and abstract alone, unrelated intervention or comparator ($n = 76$), incomplete study data ($n = 30$), or being an animal study ($n = 13$). The remaining 34 citations had their full-text reviewed. Of these, 25 were excluded because of irrelevant comparator ($n = 2$), not being an RCT ($n = 20$), and being a protocol without results ($n = 3$). Consequently, nine RCTs [13–21] involving a total of 1806 patients were found to be suitable for this meta-analysis. The search process is shown in Fig. 1. The authors of one of these studies reported potential conflicts of interest related to industry sponsorship [19].

Characteristics of Included Studies

Eight RCTs [13, 15–21] were multicentric, while one trial [14] was performed at a single center. Two studies [15, 17] belong to the subgroup analysis of the STOP! trial [16], while the data for two more studies [20, 21] were obtained from the MEDITA trial [18]. Two trials [16, 17] involved adolescents while the remaining seven trials [13–15, 18–21] only involved adults. All trials [13–21] enrolled patients presenting with any trauma severity treated at a hospital ED. The majority of the included patients exhibited moderate-to-severe trauma, but three studies investigated patients with severe pain [14], moderate pain [15], and minor-to-moderate

pain [16] (see Table 1 for more details regarding trauma severity from included trials). Specification of the methoxyflurane dosage was the same for all the included trials with the most common regimen being a Penthrox® inhaler (containing 3 mL methoxyflurane). However, the intervention methods of the control group varied among studies: four trials [15–17, 19] were normal saline controlled, while five trials [13, 14, 18, 20, 21] used different SAT modes. Specially, one study [19] added the SAT in both experimental and normal saline groups. Detailed characteristics of all the included studies are shown in Table 1.

Risk of Bias

The risk of bias assessment for all nine studies can be viewed in the supplemental material (eTable 2, eFig. 1A, B). The overall risk of bias was low in four double-blind RCTs [15–17, 19], and high in five open label trials [13, 14, 18, 20, 21] because participants or investigators were not blinded. All included trials exhibited prespecified outcomes. Randomization sequences and concealed allocation were adequately generated in all studies. Three trials [18, 20, 21] had an unclear risk of other bias that was attributed to a lack of sufficient methodological reports.

Primary Outcomes

Seven trials [13, 15–18, 20, 21] reported on the change in pain intensity score within 30 min after the start of treatment. Pain intensity change was reported using a 100-point VAS (six studies, $n = 1028$) [15–18, 20, 21] or NRS (1 study, $n = 305$) [13], which was converted to a 10-point scale. One of the seven trials was not included in the meta-analysis because we were unable obtain the original data from graphs [20]. Changes in pain intensities were analyzed several times from baseline to 3 min (three studies, $n = 668$) [13, 18, 21], 5 min (six studies, $n = 1264$) [13, 15–18, 21], 10 min (six studies, $n = 1264$) [13, 15–18, 21], 15 min (six studies, $n = 1264$) [13, 15–18, 21], 20 min (six studies, $n = 1264$) [13, 15–18, 21], 25 min (two studies,
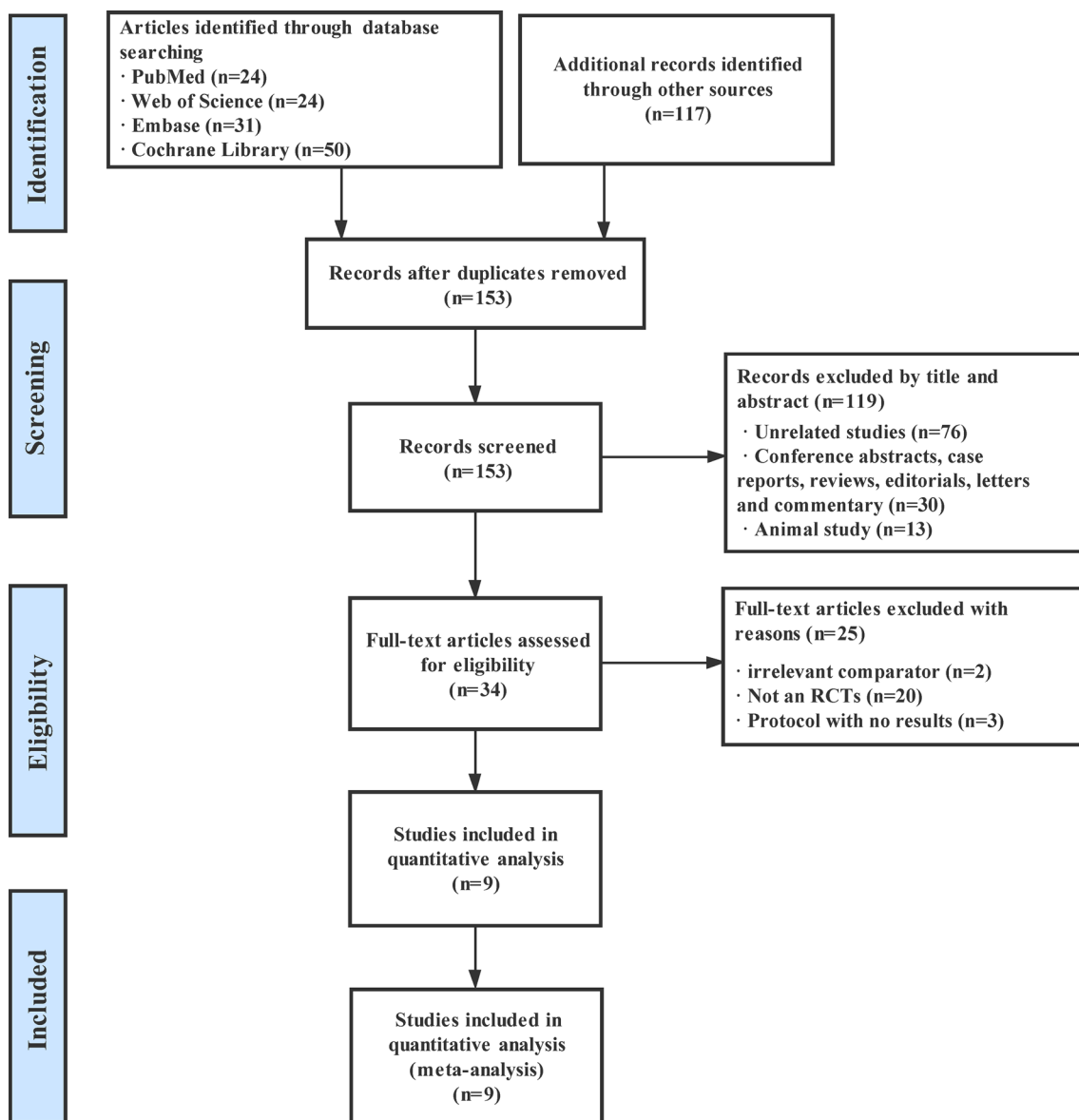
Fig. 1 Study flowchart

$n = 363$) [18, 21], and 30 min (two studies, $n = 363$) [18, 21] to assess the pooled effects.

Participants administered methoxyflurane exhibited larger mean reduction from baseline in pain intensity score than the control group at 3 min (WMD − 0.44 cm; 99% CI − 0.64, − 0.23; $p < 0.00001$; $I^2 = 0$%), 5 min (WMD − 0.93 cm; 99% CI − 1.14, − 0.71; $p < 0.00001$; $I^2 = 28$%), 10 min (WMD − 1.11 cm; 99% CI − 1.56, − 0.66; $p < 0.00001$; $I^2 = 65$%), 15 min (WMD − 1.23 cm; 99% CI − 1.99, − 0.47;

$p < 0.0001$; $I^2 = 85$%), and 20 min (WMD − 1.12 cm; 99% CI − 1.75, − 0.49; $p < 0.00001$; $I^2 = 75$%). Changes in pain intensity did not differ between groups at 25 min (WMD − 0.36 cm; 99% CI − 0.85, 0.31; $p = 0.06$; $I^2 = 3$%) and 30 min (WMD − 0.39 cm; 99% CI − 0.97, 0.19; $p = 0.08$; $I^2 = 0$%) (Figs. 2, 3a, b). These differences failed to meet the threshold for clinical significance (a 1.3- to 1.5-cm change at any single time point).

Table 1 Baseline characteristics of included studies

Study	Study design	Study population	Methoxyflurane group (n)	Control group (n)	Primary outcome	Secondary outcome
Borobia [13]	Multisite RCT	Age ≥ 18 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose (156)	SAT: NSAIDs for moderate pain; nonopioid and opioid for severe pain (149)	Change in NRS scores at 3, 5, 10, 15, 20 min	(1) Time from the start of treatment to first pain relief (2) Number of first pain relief (3) Proportion of rescue analgesic medication (4) TEAEs (5) Satisfaction measurement of patients
Brichko [14]	Single-site RCT	Age 18–75 years; trauma with severe acute pain treated at a hospital ED (NRS ≥ 8)	3 mL inhaled dose (60)	SAT: multimodal approach including nonopioid and opioid (60)	Number of pain relief (reduction of NRS score by ≥ 50%)	(1) NRS scores at 15, 30, 60, 90 min (no baseline value) (2) TEAEs (no specific data)
Coffey [15]	Multisite RCT	Age ≥ 12 years; trauma with minor-to-moderate acute pain treated at a hospital ED (1 ≤ NRS < 7)	3 mL inhaled dose (149)	5 mL normal saline inhaled (149)	Change in VAS scores at 5, 10, 15, 20, 30 min	(1) Time from the start of treatment to first pain relief (2) Proportion of rescue analgesic medication (3) TEAEs (4) Satisfaction measurement of patients, physician, and nurse

Table 1 continued

Study	Study design	Study population	Methoxyflurane group (*n*)	Control group (*n*)	Primary outcome	Secondary outcome
Coffey [16]	Subgroup analysis of multisite RCT	Age ≥ 18 years; trauma with moderate acute pain treated at a hospital ED (4 ≤ NRS < 7)	3 mL inhaled dose (102)	5 mL normal saline inhaled (101)	Change in VAS scores at 5, 10, 15, 20 min	(1) Time from the start of treatment to first pain relief (2) Number of first pain relief (3) Proportion of rescue analgesic medication (4) TEAEs (5) Satisfaction measurement of patients, physician, and nurse
Hartshorn [17]	Subgroup analysis of multisite RCT	Age 12–17 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose (47)	5 mL normal saline inhaled (48)	Change in VAS scores at 5, 10, 15, 20 min	(1) Time from the start of treatment to first pain relief (2) Number of first pain relief (3) Proportion of rescue analgesic medication (4) TEAEs (5) Satisfaction measurement of patients, physician, and nurse

Table 1 continued

Study	Study design	Study population	Methoxyflurane group (*n*)	Control group (*n*)	Primary outcome	Secondary outcome
Mercadante [18]	Multisite RCT	Age ≥ 18 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose (135)	SAT: paracetamol or ketoprofen for moderate pain; morphine for severe pain (135)	Change in VAS scores at 3, 5, 10, 15, 20, 25, 30 min	(1) Time from the start of treatment to first pain relief (2) Number of first pain relief (3) Proportion of rescue analgesic medication (4) TEAEs (5) Satisfaction measurement of patients and physician
Ricard-Hibon [19]	Multisite RCT	Age ≥ 18 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose plus SAT (178)[a]	5 mL normal saline inhaled plus SAT (173)[a]	Time from the start of treatment to pain relief (insufficient data)	(1) Number of first pain relief (2) TEAEs (3) Satisfaction measurement of patients, physician, and nurse

Table 1 continued

Study	Study design	Study population	Methoxyflurane group (n)	Control group (n)	Primary outcome	Secondary outcome
Serra [20]	Subgroup analysis of multisite RCT	Age ≥ 65 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose (35)	SAT: paracetamol or ketoprofen for moderate pain; morphine for severe pain (34)	Change in VAS scores at 3, 5, 10, 15, 20, 25, 30 min	(1) Time from the start of treatment to first pain relief (2) Number of first pain relief (3) Proportion of rescue analgesic medication (4) Adverse events (not TEAE) (5) Satisfaction measurement of patients and physician
Voza [21]	Subgroup analysis of multisite RCT	Age ≥ 18 years; trauma with moderate-to-severe acute pain treated at a hospital ED (NRS ≥ 4)	3 mL inhaled dose (49)	SAT: paracetamol or ketoprofen for moderate pain; morphine for severe pain (44)	Change in VAS scores at 3, 5, 10, 15, 20, 25, 30 min	(1) Time from the start of treatment to first pain relief (2) Proportion of rescue analgesic medication (3) TEAEs (4) Satisfaction measurement of patients and physician

n number of patients, *NSAIDs* non-steroidal anti-inflammatory drugs, *RCT* randomized controlled trial, *ED* emergency department, *SAT* standard analgesic treatment, *NRS* numeric rating scales, *VAS* visual analogue scale, *TEAEs* treatment-emergent adverse events

[a] Any type and route of analgesic was permitted according to the protocol in each center, except strong oral opioids and analgesics administered intranasally

3 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
Borobia 2020	-1.45	1.16	156	-0.89	1.16	149	36.0%	-0.56 [-0.90, -0.22]
Mercadante 2019	-0.63	0.97	135	-0.26	0.97	135	45.6%	-0.37 [-0.67, -0.07]
Voza 2020	-0.469	0.898	49	-0.096	0.8947	44	18.4%	-0.37 [-0.85, 0.11]
Total (99% CI)			340			328	100.0%	-0.44 [-0.64, -0.23]

Heterogeneity: Chi² = 1.30, df = 2 (P = 0.52); I² = 0%
Test for overall effect: Z = 5.50 (P < 0.00001)

Mean Difference — IV, Fixed, 99% CI — Favours [methoxyflurane] / Favours [control]

5 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
Borobia 2020	-1.98	1.38	156	-1.17	1.39	149	27.8%	-0.81 [-1.22, -0.40]
Coffey 2014	-2.31	1.67	149	-1.13	1.67	149	18.7%	-1.18 [-1.68, -0.68]
Coffey 2016	-2.07	1.56	102	-0.8	1.56	101	14.6%	-1.27 [-1.83, -0.71]
Hartshorn 2019	-2.45	1.89	47	-1.46	1.89	48	4.6%	-0.99 [-1.99, 0.01]
Mercadante 2019	-1.485	1.357	135	-0.799	1.357	135	25.6%	-0.69 [-1.11, -0.26]
Voza 2020	-1.489	1.36	49	-0.626	1.36	44	8.8%	-0.86 [-1.59, -0.14]
Total (99% CI)			638			626	100.0%	-0.93 [-1.14, -0.71]

Heterogeneity: Chi² = 6.91, df = 5 (P = 0.23); I² = 28%
Test for overall effect: Z = 11.09 (P < 0.00001)

Mean Difference — IV, Fixed, 99% CI — Favours [methoxyflurane] / Favours [control]

10 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
Borobia 2020	-2.62	1.6	156	-1.33	1.6	149	20.8%	-1.29 [-1.76, -0.82]
Coffey 2014	-2.89	1.89	149	-1.48	1.89	149	19.0%	-1.41 [-1.97, -0.85]
Coffey 2016	-2.74	1.85	102	-1.11	1.85	101	16.9%	-1.63 [-2.30, -0.96]
Hartshorn 2019	-2.81	1.96	47	-1.88	1.96	48	11.1%	-0.93 [-1.97, 0.11]
Mercadante 2019	-2.3	1.65	135	-1.58	1.65	135	19.9%	-0.72 [-1.24, -0.20]
Voza 2020	-2.19	1.76	49	-1.76	1.76	44	12.3%	-0.43 [-1.37, 0.51]
Total (99% CI)			638			626	100.0%	-1.11 [-1.56, -0.66]

Heterogeneity: Tau² = 0.11; Chi² = 14.17, df = 5 (P = 0.01); I² = 65%
Test for overall effect: Z = 6.39 (P < 0.00001)

Mean Difference — IV, Random, 99% CI — Favours [methoxyflurane] / Favours [control]

15 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
Borobia 2020	-2.89	1.6	156	-1.45	1.6	149	19.0%	-1.44 [-1.91, -0.97]
Coffey 2014	-3.4	2.16	149	-1.55	2.16	149	17.9%	-1.85 [-2.49, -1.21]
Coffey 2016	-3.33	2.11	102	-1.23	2.11	101	17.0%	-2.10 [-2.86, -1.34]
Hartshorn 2019	-3.16	2.36	47	-1.92	2.36	48	13.2%	-1.24 [-2.49, 0.01]
Mercadante 2019	-2.85	1.86	135	-2.32	1.86	135	18.3%	-0.53 [-1.11, 0.05]
Voza 2020	-2.73	2.22	49	-2.68	1.79	44	14.6%	-0.05 [-1.12, 1.02]
Total (99% CI)			638			626	100.0%	-1.23 [-1.99, -0.47]

Heterogeneity: Tau² = 0.42; Chi² = 33.30, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 4.18 (P < 0.0001)

Mean Difference — IV, Random, 99% CI — Favours [methoxyflurane] / Favours [control]

20 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 99% CI
Borobia 2020	-3.19	1.69	156	-1.89	1.69	149	20.5%	-1.30 [-1.80, -0.80]
Coffey 2014	-3.5	2.33	149	-1.9	2.33	149	18.3%	-1.60 [-2.30, -0.90]
Coffey 2016	-3.48	2.33	102	-1.52	2.33	101	16.5%	-1.96 [-2.80, -1.12]
Hartshorn 2019	-3.17	2.34	47	-2.37	2.34	48	12.3%	-0.80 [-2.04, 0.44]
Mercadante 2019	-3.25	1.98	135	-2.66	1.98	135	19.1%	-0.59 [-1.21, 0.03]
Voza 2020	-3.34	2.25	49	-3.15	2.01	44	13.3%	-0.19 [-1.33, 0.95]
Total (99% CI)			638			626	100.0%	-1.12 [-1.75, -0.49]

Heterogeneity: Tau² = 0.26; Chi² = 20.13, df = 5 (P = 0.001); I² = 75%
Test for overall effect: Z = 4.56 (P < 0.00001)

Mean Difference — IV, Random, 99% CI — Favours [methoxyfluranel] / Favours [control]

25 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
Mercadante 2019	-3.66	1.56	135	-3.21	1.89	135	81.7%	-0.45 [-0.99, 0.09]
Voza 2020	-3.84	2.33	49	-3.89	1.96	44	18.3%	0.05 [-1.10, 1.20]
Total (99% CI)			184			179	100.0%	-0.36 [-0.85, 0.13]

Heterogeneity: Chi² = 1.03, df = 1 (P = 0.31); I² = 3%
Test for overall effect: Z = 1.88 (P = 0.06)

Mean Difference — IV, Fixed, 99% CI — Favours [methoxyflurane] / Favours [control]

30 minutes

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Fixed, 99% CI
Mercadante 2019	-4.07	2.16	135	-3.56	2.16	135	73.7%	-0.51 [-1.19, 0.17]
Voza 2020	-4.4	2.34	49	-4.34	1.9	44	26.3%	-0.06 [-1.19, 1.07]
Total (99% CI)			184			179	100.0%	-0.39 [-0.97, 0.19]

Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%
Test for overall effect: Z = 1.74 (P = 0.08)

Mean Difference — IV, Fixed, 99% CI — Favours [methoxyflurane] / Favours [control]

◄**Fig. 2** Forest plots of the change in pain intensity score at different times within 30 min after the start of treatment. SD standard deviation, IV inverse-variance method, Tau^2 a variance of the effect size across studies, Chi^2 a test of significance for heterogeneity, I^2 a test for heterogeneity where highest level is 100%, Z a significance test for the weighted average effect size. A low P value or large Chi^2 relative to its degree of freedom (df) provides evidence of heterogeneity of intervention effects. The squares and bars represent the mean values and 99% CIs of the effect sizes, and the area of the squares reflects the weight of the studies. The diamond represents the combined effect

Secondary Pain-Related Outcomes

Time from Start of Treatment to First Pain Relief

Seven studies [13, 15, 16, 18, 20, 21, 25] reported the time of first pain relief, and one of these seven trials was not included in the meta-analysis because of insufficient information to allow for analysis [15]. Compared to the control group, methoxyflurane was shown to significantly shorten the time to first pain relief by an average of 5.29 min (95% CI − 6.97 min to − 3.62 min; $p < 0.00001$; $I^2 = 100\%$) (Fig. 4a).

Proportion of Patients Experiencing Pain Relief

The proportion of pain relief was assessed in six studies [13, 15, 17–20]. Patients in the methoxyflurane group exhibited higher pain relief rates than the control group (RR 1.41; 95% CI 1.17–1.70; $p = 0.0003$; $I^2 = 85\%$) (Fig. 4b).

Proportion of Patients Administered Rescue Analgesic Medication

Seven studies [13, 15–18, 20, 21] reported the proportions of patients administered the rescue
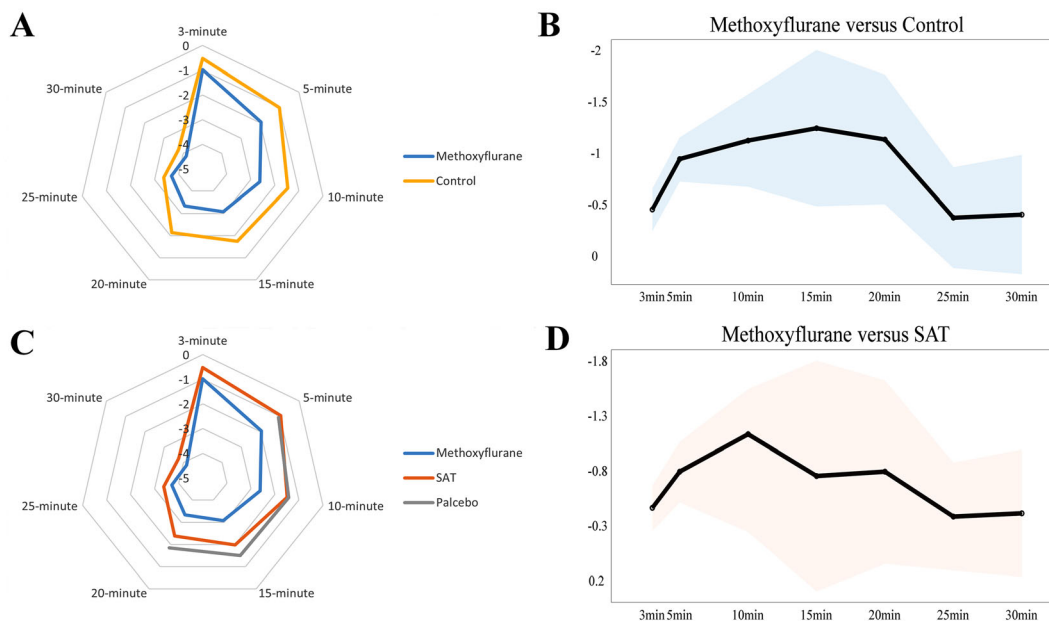
Fig. 3 a Star plot for weighted mean of the change in pain scores across 30 min at seven time points in methoxyflurane and control groups. **b** Band plot for weighted mean difference (WMD) of the change in pain severity scores across 30 min at seven time points (3 min, 5 min, 10 min, 15 min, 20 min, 25 min, and 30 min) between methoxyflurane versus control. **c** Star plot for weighted mean of the change in pain scores across 30 min at seven time points in methoxyflurane, placebo, and SAT groups. **d** Band plot for weighted mean difference (WMD) of the change in pain severity scores across 30 min at seven time points (3 min, 5 min, 10 min, 15 min, 20 min, 25 min, and 30 min) between methoxyflurane versus SAT. SAT standard analgesic treatment; pooled estimates of the WMD for each time point are represented by the dark line and 99% CIs are represented by surrounding shaded region
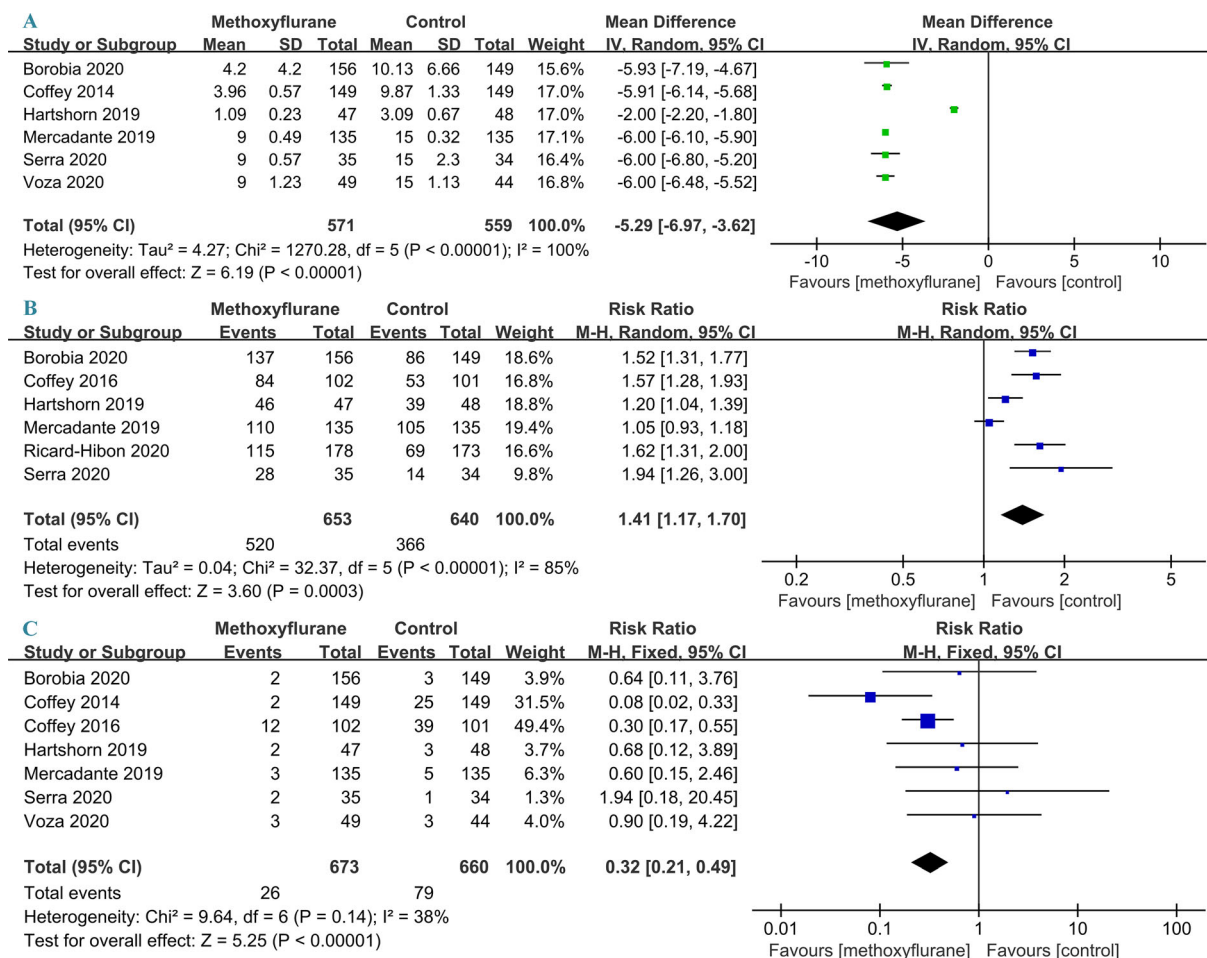
A

Study or Subgroup	Methoxyflurane Mean	SD	Total	Control Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Borobia 2020	4.2	4.2	156	10.13	6.66	149	15.6%	-5.93 [-7.19, -4.67]
Coffey 2014	3.96	0.57	149	9.87	1.33	149	17.0%	-5.91 [-6.14, -5.68]
Hartshorn 2019	1.09	0.23	47	3.09	0.67	48	17.0%	-2.00 [-2.20, -1.80]
Mercadante 2019	9	0.49	135	15	0.32	135	17.1%	-6.00 [-6.10, -5.90]
Serra 2020	9	0.57	35	15	2.3	34	16.4%	-6.00 [-6.80, -5.20]
Voza 2020	9	1.23	49	15	1.13	44	16.8%	-6.00 [-6.48, -5.52]
Total (95% CI)			571			559	100.0%	-5.29 [-6.97, -3.62]

Heterogeneity: Tau² = 4.27; Chi² = 1270.28, df = 5 (P < 0.00001); I² = 100%
Test for overall effect: Z = 6.19 (P < 0.00001)

B

Study or Subgroup	Methoxyflurane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borobia 2020	137	156	86	149	18.6%	1.52 [1.31, 1.77]
Coffey 2016	84	102	53	101	16.8%	1.57 [1.28, 1.93]
Hartshorn 2019	46	47	39	48	18.8%	1.20 [1.04, 1.39]
Mercadante 2019	110	135	105	135	19.4%	1.05 [0.93, 1.18]
Ricard-Hibon 2020	115	178	69	173	16.6%	1.62 [1.31, 2.00]
Serra 2020	28	35	14	34	9.8%	1.94 [1.26, 3.00]
Total (95% CI)		653		640	100.0%	1.41 [1.17, 1.70]
Total events	520		366			

Heterogeneity: Tau² = 0.04; Chi² = 32.37, df = 5 (P < 0.00001); I² = 85%
Test for overall effect: Z = 3.60 (P = 0.0003)

C

Study or Subgroup	Methoxyflurane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Borobia 2020	2	156	3	149	3.9%	0.64 [0.11, 3.76]
Coffey 2014	2	149	25	149	31.5%	0.08 [0.02, 0.33]
Coffey 2016	12	102	39	101	49.4%	0.30 [0.17, 0.55]
Hartshorn 2019	2	47	3	48	3.7%	0.68 [0.12, 3.89]
Mercadante 2019	3	135	5	135	6.3%	0.60 [0.15, 2.46]
Serra 2020	2	35	1	34	1.3%	1.94 [0.18, 20.45]
Voza 2020	3	49	3	44	4.0%	0.90 [0.19, 4.22]
Total (95% CI)		673		660	100.0%	0.32 [0.21, 0.49]
Total events	26		79			

Heterogeneity: Chi² = 9.64, df = 6 (P = 0.14); I² = 38%
Test for overall effect: Z = 5.25 (P < 0.00001)

Fig. 4 Forest plots of secondary outcomes associated with pain. **a** Time of first pain relief; **b** proportion of patients experiencing pain relief until their departure from the emergency department; **c** proportion of patients who received rescue analgesic medication before discharge. SD standard deviation, IV inverse-variance method, M-H the Mantel–Haenszel method, Tau² a variance of the effect size across studies, Chi² a test of significance for heterogeneity, I^2 a test for heterogeneity where highest level is 100%, Z a significance test for the weighted average effect size. A low p value or large Chi² relative to its degree of freedom (df) provides evidence of heterogeneity of intervention effects. The squares and bars represent the mean values and 95% CIs of the effect sizes. The diamond represents the combined effect

analgesic medication before discharge, and all studies had complete data to allow statistical analysis. Compared to the control group, inhaled methoxyflurane significantly reduced the proportion of patients administered the rescue analgesic medication (RR 0.32; 95% CI 0.21–0.49; $p < 0.00001$; $I^2 = 38\%$) (Fig. 4c).

Other Secondary Outcomes

Proportions of Patients, Physicians, or Nurses Who Rated Satisfaction as Excellent, Very Good, or Good

For therapeutic satisfaction, eight studies [13, 15–21], seven studies [15–21], and four studies [15–17, 19] reported the proportion of patients, physicians, and nurses that rated it as excellent, very good, or good, respectively. One study [16] was excluded because its data were
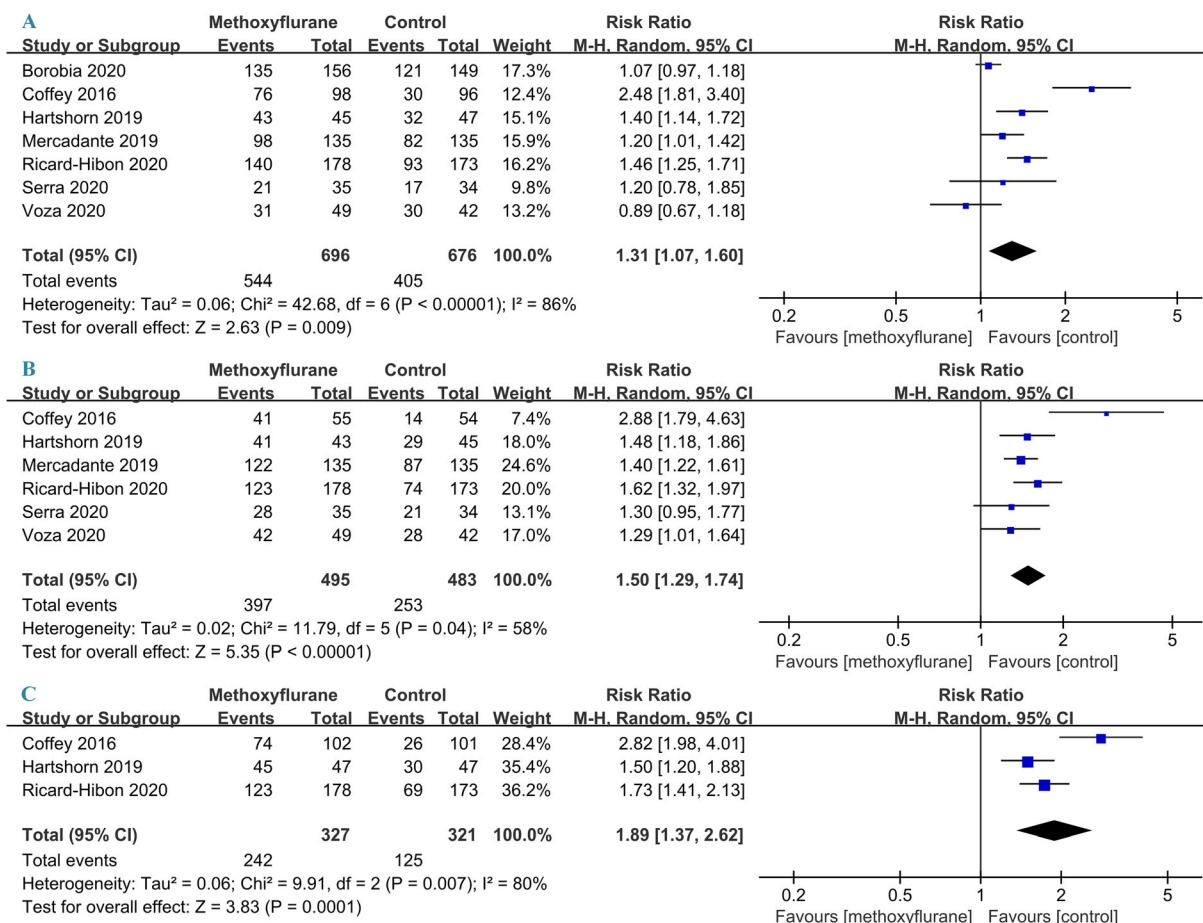
A

Study or Subgroup	Methoxyflurane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Borobia 2020	135	156	121	149	17.3%	1.07 [0.97, 1.18]
Coffey 2016	76	98	30	96	12.4%	2.48 [1.81, 3.40]
Hartshorn 2019	43	45	32	47	15.1%	1.40 [1.14, 1.72]
Mercadante 2019	98	135	82	135	15.9%	1.20 [1.01, 1.42]
Ricard-Hibon 2020	140	178	93	173	16.2%	1.46 [1.25, 1.71]
Serra 2020	21	35	17	34	9.8%	1.20 [0.78, 1.85]
Voza 2020	31	49	30	42	13.2%	0.89 [0.67, 1.18]
Total (95% CI)		**696**		**676**	**100.0%**	**1.31 [1.07, 1.60]**
Total events	544		405			

Heterogeneity: Tau² = 0.06; Chi² = 42.68, df = 6 (P < 0.00001); I² = 86%
Test for overall effect: Z = 2.63 (P = 0.009)

B

Study or Subgroup	Methoxyflurane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Coffey 2016	41	55	14	54	7.4%	2.88 [1.79, 4.63]
Hartshorn 2019	41	43	29	45	18.0%	1.48 [1.18, 1.86]
Mercadante 2019	122	135	87	135	24.6%	1.40 [1.22, 1.61]
Ricard-Hibon 2020	123	178	74	173	20.0%	1.62 [1.32, 1.97]
Serra 2020	28	35	21	34	13.1%	1.30 [0.95, 1.77]
Voza 2020	42	49	28	42	17.0%	1.29 [1.01, 1.64]
Total (95% CI)		**495**		**483**	**100.0%**	**1.50 [1.29, 1.74]**
Total events	397		253			

Heterogeneity: Tau² = 0.02; Chi² = 11.79, df = 5 (P = 0.04); I² = 58%
Test for overall effect: Z = 5.35 (P < 0.00001)

C

Study or Subgroup	Methoxyflurane Events	Total	Control Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Coffey 2016	74	102	26	101	28.4%	2.82 [1.98, 4.01]
Hartshorn 2019	45	47	30	47	35.4%	1.50 [1.20, 1.88]
Ricard-Hibon 2020	123	178	69	173	36.2%	1.73 [1.41, 2.13]
Total (95% CI)		**327**		**321**	**100.0%**	**1.89 [1.37, 2.62]**
Total events	242		125			

Heterogeneity: Tau² = 0.06; Chi² = 9.91, df = 2 (P = 0.007); I² = 80%
Test for overall effect: Z = 3.83 (P = 0.0001)

Fig. 5 Forest plot of the proportion of different evaluators for satisfaction assessment who rated as excellent, very good, or good. **a** Patient assessment; **b** physician assessment; **c** research nurse assessment. *M-H* the Mantel–Haenszel method, Tau^2 a variance of the effect size across studies, Chi^2 a test of significance for heterogeneity, I^2 a test for heterogeneity where highest level is 100%, Z a significance test for the weighted average effect size. A low p value or large Chi^2 relative to its degree of freedom (*df*) provides evidence of heterogeneity of intervention effects. The squares and bars represent the mean values and 95% CIs of the effect sizes. The diamond represents the combined effect

not available in an extractable format. Compared to the control group, the overall efficacy of methoxyflurane was rated excellent, very good, or good by significantly more patients in the methoxyflurane group (RR 1.31; 95% CI 1.07–1.60; $p = 0.009$; $I^2 = 86\%$). Moreover, significantly more physicians (RR 1.50; 95% CI 1.29–1.74; $p < 0.00001$; $I^2 = 58\%$) and nurses (RR 1.89; 95% CI 1.37–2.62; $p = 0.0001$; $I^2 = 80\%$) rated the practicality of using methoxyflurane as excellent, very good, or good when compared to the control (Fig. 5).

Methoxyflurane-Related TEAEs

Eight studies [13–19, 21] evaluated the total incidence of TEAEs, but one of these trials was not included because raw data were not presented in the manuscript [14]. In the meantime, the most common adverse events following methoxyflurane administration, namely, dizziness, somnolence, feeling drunk, and headache, were reported by seven (1386 patients) [13, 15, 17–21], six (1295 patients) [13, 15, 17–20], four (809 patients) [17–19, 21], and four (921 patients) [15, 17–19] of the included trials, respectively.

The risk of total TEAEs after methoxyflurane administration increased three-fold (RR 3.09; 95% CI 1.72–5.57; I^2 = 87%), and there was a statistically significant difference when compared to the control (p = 0.0002) (eFig. 2A). Pooled results showed a significantly elevated risk of dizziness (RR 4.12; 95% CI 2.69–6.29; I^2 = 0%; p < 0.00001), somnolence (RR 3.60; 95% CI 1.84–7.07; I^2 = 0%; p = 0.0002), and feeling drunk (RR 5.43; 95% CI 2.21–13.89; I^2 = 0%; p = 0.0004) in patients administered methoxyflurane, when compared to those not administered methoxyflurane. However, we found similar rates of headache (RR 1.26 [95% CI 0.81–1.95]; risk difference, 2% [95% CI − 2 to 5%]; I^2 = 0%) between those receiving and those not receiving methoxyflurane (eFig. 2B). Pooled results of TEAEs grouped by system organ (p > 0.05) and remaining occasional symptoms (p > 0.05) are presented in supplementary material eFigs. 3 and 4.

Sensitivity and Subgroup Analysis

Neither of the sensitivity analyses, one excluding the studies with a high risk of bias and the other excluding the results of the PenASAP trial [19], changed the robustness of estimates or conclusions for any outcomes of high heterogeneity. However, results of the sensitivity analysis suggest that the open-label studies were probably identified as the most dominant sources of heterogeneity for this research (supplementary material eTables 3A and 4A).

Our pre-specified subgroup analysis indicated that heterogeneity may be attributed to the age subgroup and the control group intervention methods. A pre-specified subgroup analysis comparing the change in pain intensity score at 15 and 20 min after the start of treatment on inhaled normal saline and SAT found the intervention of the control group to be an effect modifier. When excluding the data for normal saline group, subgroup analysis changed the significant overall effect of pain reduction to insignificant at 15 min [13, 18, 21] (WMD − 0.73; 99% CI − 1.78 to 0.32; p = 0.07) and 20 min [13, 18, 21] (WMD − 0.77; 99% CI − 1.60 to 0.07; p = 0.02 > 0.01) (Fig. 3c, d); in

other words, there was no significant improvement in pain intensity at 15 min and 20 min for the group administered methoxyflurane when compared to SAT (supplementary material eTable 3B). Subsequent subgroup analysis for secondary pain-related outcomes showed that the superiority of methoxyflurane was further narrowed when compared to SAT (the p values were close to the threshold). The different onset time of the two analgesia methods might explain why the overall analgesic benefit of methoxyflurane is not superior to SAT (WMD − 6.00 min; 99% CI − 6.10 to − 5.90; p < 0.0001) [13, 18, 20, 21]. Interestingly, adolescents were shown to exhibit better tolerance to methoxyflurane when compared to adults because of higher satisfactory level (RR 1.40 vs RR 1.29) and lower TEAEs incidence (RR 1.39 vs RR 4.45) was observed according to the results of another pre-defined subgroup analysis (supplementary material eTable 4B).

Quality of Evidence

Table 2 shows the summary of findings for all outcomes including the certainty of evidence. The quality of evidence was downgraded by the high risk of bias, serious inconsistency with high heterogeneity (I^2 > 50%), or serious imprecision with wide CI in the results. The quality of evidence was low or very low in most outcomes. The outcome of nurses' satisfaction assessment was the only one that exhibited a moderate quality of evidence.

DISCUSSION

Our findings show that inhaled methoxyflurane compared with control was significantly associated with a statistically significant but clinically unimportant improvement in pain relief for patients with trauma-associated pain during the first 20 min, and without lasting effects at 25 min and 30 min. Although patients and their healthcare providers exhibited a high level of methoxyflurane treatment satisfaction, methoxyflurane significantly increased the risk of non-serious TEAEs, especially dizziness, somnolence, and feeling drunk. These results

Table 2 GRADE summary of findings

Outcomes	No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence
Primary outcome							
Change in pain intensity score within 30 min after the start of treatment							
At 3 min	668 (3 RCTs)	Very serious[a]	Not serious	Not serious	Serious[c]	None	⊕◯◯◯ Very low
At 5 min	1264 (6 RCTs)	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low
At 10 min	1264 (6 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low
At 15 min	1264 (6 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low
At 20 min	1264 (6 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low
At 25 min	363 (2 RCTs)	Very serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low
At 30 min	363 (2 RCTs)	Very serious[a]	Not serious	Not serious	Serious[c]	None	⊕◯◯◯ Very low
Secondary pain-related outcomes							
Time from the start of treatment to first pain relief	1130 (6 RCTs)	Serious[a]	Very serious[b]	Not serious	Not serious	None	⊕◯◯◯ Very low
Proportion of patients experiencing pain relief	1293 (6 RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕◯◯ Low
Proportion of patients administered rescue analgesic medication	1333 (7 RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕◯◯ Low
Proportions of patients, physicians, or nurses who rated satisfaction as excellent, very good, or good							
Proportion of patients	1372 (7 RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕◯◯ Low
Proportion of physicians	978 (6 RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	None	⊕⊕◯◯ Low

Table 2 continued

Outcomes	No. of participants (studies)	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Certainty of the evidence
Proportion of nurses	648 (3 RCTs)	Not serious	Serious[b]	Not serious	Not serious	None	⊕⊕⊕◯ Moderate
Methoxyflurane-related TEAEs							
Total incidence of TEAEs	1615 (7 RCTs)	Serious[a]	Serious[b]	Not serious	Serious[c]	None	⊕◯◯◯ Very low
Dizziness	1386 (7 RCTs)	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low
Somnolence	1295 (6 RCTs)	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low
Feeling drunk	809 (4 RCTs)	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low
Headache	921 (4 RCTs)	Serious[a]	Not serious	Not serious	Serious[c]	None	⊕⊕◯◯ Low

GRADE Grading of Recommendations, Assessment, Development and Evaluation, *No.* number, *RCTs* randomized controlled trials, *TEAEs* treatment-emergent adverse events

[a] Downgraded because of the studies with high risk of bias (open-label trial)

[b] Downgraded because of substantial statistical heterogeneity of $I^2 > 50\%$

[c] Downgraded because of a wide confidence interval of the results

were still robust in sensitivity analysis by excluding the open-label studies, which had a high risk of bias. Important to note is that superiority of the analgesic advantage of methoxyflurane was weak and not particularly pronounced when compared to SAT in our pre-defined subgroup analysis; conversely, inhaled methoxyflurane was significantly associated with superior and faster pain relief for patients with trauma-associated pain when compared to inhaled normal saline. These findings help to inform one of the most controversial issues; that is, whether inhaled methoxyflurane implements fast and efficient pain management in trauma patients [25].

Pain is one of the most common complications that requires prompt management in emergency medicine [2]. Approximately 60–90% of the patients in the ED present with acute trauma pain, which is one of the main reasons why patients seek treatment [43, 44].

However, there are no consolidated pain management practices, and acute postoperative pain is still a problem for clinicians [45]. Methoxyflurane is a halogenated ether that is administered through a portable inhaler [12], and the minimum alveolar concentration (MAC) value of methoxyflurane (0.16%) was the smallest compared to sevoflurane (2.00%), isoflurane (1.15%), and desflurane (6.00%). It has a rapid analgesic effect and is recommended as an emergency treatment option for patients with trauma and associated pain. Previously, the relationship between inhaled methoxyflurane and clinical outcomes of trauma pain had been elucidated by observational studies and some review studies of non-quantitative analysis. Recently, data from multicenter RCTs has significantly expanded the evidence base, but yielded discrepant results. Borobia et al. [13] reported that pain relief for patients in the methoxyflurane treatment group was superior

compared to that of individuals in the standard therapy group. However, their conclusions were seemingly inconsistent with another several trials, and this inconsistency was more conspicuous in safety findings [14, 20, 21]. Moreover, methoxyflurane has not been widely recognized and there is no global consensus for its use as a therapeutic option [25, 26]. Therefore, an objective meta-analysis study should be performed on the basis of the findings of the current RCT studies.

In this meta-analysis, we comprehensively assessed the analgesic capacity of methoxyflurane through the change in pain intensity at multiple time points, the time to first pain relief, the first pain relief rate, and the rescue analgesia rate. Although pain scores reported by patients are subjective, the other three metrics can be used as objective complementary items for assessing pain intensity [46]. A lower rescue analgesia rate or a higher first pain relief rate may indicate a lower pain intensity; and in terms of pain score, the VAS and NRS were used as the evaluation method for all included studies, which is very important for reducing clinical heterogeneity [46, 47]. Although the aforementioned factors guarantee data integrity and objectivity in our study, the reduction range of mean difference in pain intensity between the two groups within the first 20 min at different time points was from 0.9 to 1.2 points, which is likely to only represent a marginal clinically relevant improvement. Studies have reported that a clinically meaningful difference in efficacy between two treatments should be at least 1.3 points on NRS and 1.5 points for older ED patients [39, 40]. However, there is no consensus with regard to the minimum clinically important difference in pain intensity, with marked differences between studies [48, 49]. On the basis of the aforementioned reasons, and considering the significantly quicker time to first pain relief and the favorable patient- and health personnel-reported assessments of satisfaction, we concluded that methoxyflurane inhalation is a faster pain reliever, is easy to administer, and is a potentially effective analgesic regimen for traumatic pain management in emergency settings; however, caution is warranted in its use.

Our findings demonstrate an increased risk of TEAEs, especially central nervous system-type reactions such as dizziness, somnolence, and feeling drunk that are associated with the administration of methoxyflurane [24]. This finding is consistent with that of most current RCTs examining the efficacy of methoxyflurane in trauma pain [14–17, 20, 21]. The majority of these adverse events were transient, mild, and resolved within the same day [13]. Laboratory tests performed shortly after methoxyflurane administration also revealed no evidence of nephrotoxicity or hepatotoxicity [13, 50]. However, the net analgesic effect of methoxyflurane realized should be one of the directions of future translational medicine research. The net analgesic effect is strongly associated with a significant reduction in methoxyflurane-associated adverse drug reactions [50]. As it is with the multimodal analgesia principle, it may be suitable to add aromatic adjuvant drugs (e.g., lemon, lavender, and rose) in the inhalation device in order to alleviate the central nervous symptoms [51, 52].

In addition to being safe, the cost-effective implications of methoxyflurane should also be considered [24]. Some clinicians may not administer methoxyflurane because of the high costs and a lack of clear clinical benefits, while others may choose to administer methoxyflurane for traumas that are easy to treat (e.g.,, dislocations and fractures) [24]. It has been finitely documented that the administration of inhaled methoxyflurane reduces the use of human resources and consumables compared to SAT [24, 53]. For example, Fabbri et al. suggested that the use of inhaled methoxyflurane compared with intravenously administered paracetamol plus intravenously administered morphine would lead to a reduced use of human resources and consumables, with a lower cost per process of more than 30 € (not considering the cost of the device) [24]. Another study showed the overall cost of methoxyflurane use is 86 € (considering the staff costs and the cost of device). In general, the use of methoxyflurane will be a potential saving of 96 € for each patient with upper limb/shoulder injuries [54]. However, studies included in this meta-analysis did not present any pharmaco-

economic related data. Therefore, it could be one of the key reasons contributing to the non-routine use and calling into question of methoxyflurane in the world.

Although sensitivity analyses revealed that effect estimates were robust, it is possible that certain subgroups of patients may benefit less from methoxyflurane. Our subgroup analyses comparing the effect estimates for methoxyflurane and SAT showed that methoxyflurane did not confer additional clinical benefits for patients beyond 10 min after treatment; that is, the advantages of methoxyflurane in traumatic analgesia may be minor and limited compared to SAT. This finding was confirmed by the subsequent subgroup analyses of satisfaction assessment and TEAE incidence. This difference may be attributed to the time to onset of the two analgesic methods [48]. These results contrast with those of a previous trial [13], which suggested that methoxyflurane has a superior efficacy when compared to the SAT. The results, however, have only allowed us to determine that speed of methoxyflurane action is faster. Moreover, we found that adolescents exhibited better tolerance to methoxyflurane when compared to adults according to the results of another pre-defined subgroup analysis. This underlying phenomenon could be attributed to the fact that teenagers are more susceptible to the distinctive fruity odor of methoxyflurane [17]. More studies should evaluate the role of methoxyflurane in populations of different ages.

The strengths of this meta-analysis include a pre-registered protocol, the comprehensive search strategy, and conservative GRADE assessment of certainty of evidence. The results were cautiously interpreted in the context of clinically important differences [32, 55, 56], allowing a meaningful estimate of the efficacy of methoxyflurane. Additionally, the adjusted statistical threshold for primary outcomes served to reduce the risk of type I error and multiple testing bias [32, 38]. Finally, the sensitivity analysis, by excluding a study with potential multiple risks (e.g., industry-sponsored), revealed that the effect estimates were robust, as the excluded data did not significantly influence the initial analysis.

However, there were several notable limitations. First, evidence for almost all outcomes was of low or very low quality because of high risk of bias, serious inconsistency, or imprecision in the results. A significant contributor to this poor quality of evidence is the open-label study, which represents an intrinsic bias. Although a double-dummy design could result in the delayed administration of the active drug and a prolonged pain duration for the traumatic patient, rigorous blind studies as designed by Coffey et al. are still feasible [15, 16]. Second, the current effect indicators could not evaluate the net effect of methoxyflurane. In future studies, a new comprehensive evaluation system should be established to measure the analgesic benefits and side effects of methoxyflurane. Third, we were unable to perform a publication bias test because of the small number of included studies. Finally, as a result of the small number of included trials and low quality of evidence, the findings of comparison between methoxyflurane and SAT in traumatic patients are not conclusive. With the current available data, however, the preponderance of evidence of methoxyflurane is only reflected in rapid analgesia. More adequately designed head-to-head studies are needed to assess the therapeutic differences in the efficacy of methoxyflurane vs SAT in patients with trauma pain.

CONCLUSIONS

In urgent situations without effective therapy, our systematic review and meta-analysis provides low-quality evidence that methoxyflurane may be cautiously considered as a simple, rapidly acting, and effective therapeutic option for acute trauma pain, despite the higher incidence of non-serious central nervous side effects. However, we cannot draw conclusions with enough certainty that inhaled methoxyflurane has a superior efficacy to SAT. More clinical trials focusing on the net effect of methoxyflurane vs SAT in different age populations should be performed.

ACKNOWLEDGEMENTS

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