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Effectiveness of inhaled methoxyflurane in acute pain in an emergency department – A systematic review of randomized controlled trials

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ABSTRACT

Introduction: Inhaled Methoxyflurane has emerged as a popular analgesic agent for the management of acute traumatic pain in emergency settings. The aim of this review was to assess the analgesic efficacy of methoxyflurane compared to placebo and standard analgesics.

Methods: We performed a systematic review of the literature with searches of seven databases (Medline Complete, CINAHL Complete, OVID Emcare, Embase Classic + Embase, Cochrane Library, Scopus and Web of Science Core Collection) for randomized controlled trials where patients presented to the emergency department with acute traumatic pain and were administered inhaled methoxyflurane compared to placebo or standard analgesics. The primary outcome was the effectiveness of analgesia. Secondary outcomes were adverse events and patient and clinician satisfaction.

Results: The literature search produced 250 results, of which six met the eligibility criteria. All six studies reported improved pain scores with pain reduction of up to −30.392 mm on a 100 mm VAS scale and − 5.75 on an NRS 0–10 point scale for the methoxyflurane groups. All six studies concluded a shorter time to obtain pain relief for patients in the methoxyflurane groups. Patients and clinicians reported higher satisfaction in the methoxyflurane groups and there was a low incidence of adverse events.

Conclusion: Inhaled methoxyflurane provides rapid and effective pain relief for acute trauma, consistently outperforming placebo and standard treatments and improving patient and clinician satisfaction.

1. Introduction

Effective analgesia in the Emergency Department (ED) alleviates patient suffering and supports accurate diagnostics such as X-rays and CT scans by minimizing movement and agitation. Relief from pain enables healthcare providers to complete necessary treatments and procedures more efficiently, reducing the risk of complications and improving overall patient and healthcare workers' satisfaction.

Acute pain is a common presenting complaint of patients in the ED. Timely treatment of pain is important for patient well-being, yet delays to treatment are common [1]. There are many factors associated with delays to analgesia in the ED including overcrowding, lack of resources and limited education about the importance of early analgesia as well as unclear evidence surrounding analgesic combinations [2]. Ideal analgesics should be easy to administer and effective with limited adverse effects, contraindications and abuse potential. Management of pain requires a stepwise, multi-modal approach, to improve effectiveness and efficiency. Simple analgesics such as acetaminophen (paracetamol) and non-steroidal anti-inflammatory drugs (NSAIDs) are usually the first line with opioids added in cases of severe pain.

Methoxyflurane, an anaesthetic liquid approved for human use in 1958, was almost globally discontinued due to reported incidences of

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nephrotoxicity in the 1970s [3]. However, as a low-dose inhalational anaesthetic, it has been safely used in emergency settings in Australia for decades. Since 2015 it has also been approved for use in Europe [4].

The use of inhaled methoxyflurane offers substantial advantages to healthcare staff, such as a potential reduction in intensive patient monitoring, associated workload, and length of stay when compared to alternative forms of analgesia (e.g. parenteral opioids). As such, methoxyflurane may be a viable alternative to standard analgesia for patients with acute traumatic pain in ED. Patients may prefer to use methoxyflurane over traditional analgesia because of the ease of administration and without the need for intravenous lines, which is less invasive and may be a more comfortable option. Despite this, there is a lack of high-level evidence to support inhaled methoxyflurane for acute pain in the ED.

This aim of this study was to determine the evidence supporting inhaled methoxyflurane for acute pain from randomized controlled trials in the ED setting.

2. Methods

2.1. Protocol

This systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [5,6]. The review protocol was registered with PROSPERO, registration details PROSPERO 2024 is accessible at https://www.crd.york.ac.uk/PROSPERO/view/CRD42023485958.

2.2. Search strategy

An academic librarian (MG) collaborated with the team as co-author in the process of conducting initial searches, defining the search strategy, identifying the most relevant databases, conducting and translating the searches across all the databases, using Covidence (Version 2) software to collate and remove duplication of relevant records [7] ensuring alignment with the research aim and the PICo (Problem, Intervention, Context) framework [8]. The keywords selected were methoxyflurane, analgesic, pain management, drug therapy and emergency department. Following a systematic approach to searching, after determining a clear focused question, on the effectiveness of methoxyflurane in acute pain management in an emergency department [9], these were further expanded to include synonyms attached to the key concepts.

The following seven databases were determined to be appropriate and were searched in November 2023, with the search updated in June 2024: Medline Complete, CINAHL Complete, OVID Emcare, Embase Classic + Embase, Cochrane Library, Scopus and Web of Science Core Collection. The search strategy was expanded to include subject headings from discipline-specific databases, while searches were conducted in multi-disciplinary databases with title and abstract searches. (Table 1). Phrase searching and Boolean searching (using AND for combining all three concepts and OR for synonyms) were applied in addition to using truncation within the keyword search strategy. Variations in search terms were included by adding truncation for alternative endings of words, accommodating variations in spelling, and applying acronyms where appropriate. Additional hand searching, citation tracking, and reference list checking were performed to ensure that all the available literature on the topic that included RCTs was captured. There were no date limiters in this review.

2.3. Eligibility criteria

All randomized controlled trials (RCTs) published in English, where methoxyflurane was inhaled at analgesic doses were included. These included studies where human patients presented to the ED or an emergency care setting with acute traumatic pain, any gender and patients of all ages. The comparators were placebo and standard analgesics.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	• Settings: Emergency Department • Populations: All patients presenting to the emergency department requiring analgesia for pain management • Randomized controlled trials o Intervention: administration of inhaled methoxyflurane o Control: including placebo or standard analgesia • Language of the publication: English only • Outcomes: o Analgesic effectiveness, patient and clinician satisfaction, adverse events
Exclusion criteria	• Populations outside the ED setting • Non-English publications • Route of administration other than inhalation • Use of multi-modal or breakthrough analgesia, inability to distinguish which analgesia impacts pain reduction

The exclusion criteria were populations presenting outside the emergency care setting and non-English language literature. These criteria were applied to focus the study on the emergency department management of patients with pain. All studies where the route of administration of methoxyflurane was not via inhalation, along with any studies that had multimodal analgesia in addition to methoxyflurane were excluded. Studies were ineligible for inclusion where no primary outcomes were reported.

2.4. Selection process

All references were imported into Covidence (Version 2) for processing duplicates, titles, abstracts and full-text screening. All duplicates not automatically identified by Covidence were manually identified and removed. Five reviewers (LL, HB, CJK, CJ, AA) independently screened all titles and abstracts against inclusion and exclusion criteria to identify relevant studies. Two reviewers independently assessed the full text manuscripts identified as eligible for inclusion, and any disagreements were resolved using a third reviewer based on the pre-specified inclusion and exclusion criteria.

2.5. Data extraction process

Data were extracted from the included studies by four independent reviewers (LL, HB, CJK, CJ) and collated into a data extraction spreadsheet using MS Excel. This was after a consensus was reached on the metadata extracted from selected studies. A team discussion was held to resolve any disagreements during the data extraction process. Data extracted included the characteristics of included studies where the intervention was inhaled methoxyflurane. (see Table 2).

2.6. Primary and secondary outcomes

The key outcome domains and time frame of measurement for which data were extracted, the pain score improvements, the inhalations needed or patients that required a second inhaler/rescue medication, and patient and/or staff satisfaction.

- Primary outcomes: effectiveness of analgesia and level of pain relief, and specifically, improvement of pain measured on pain score at 5 min, and within 30 min.
- Secondary outcomes: Occurrence of adverse events, patient and staff satisfaction

2.7. Risk of Bias assessment

The Cochrane Risk of Bias 2 Tool (RoB 2) as outlined in the Cochrane Handbook for Systematic Reviews, Chapter eight [10] was used. Using

the key five domains of the RoB 2, two authors screened the included studies and conflicts were resolved by a third reviewer.

2.8. Quality of evidence

The Cochrane Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [11] method was used for rating the quality of evidence for each individual study included.

3. Results

The initial search identified 249 publications from eight databases. One publication was found through citation and hand search. There were a large number of duplications, with a total of 172 removed before the screening process. During the title and abstract screening, 60 publications were excluded as they did not meet inclusion criteria, leaving 18 to undergo full-text screening. A further 10 publications did not meet inclusion criteria in this process and were excluded from the review. At the end of the screening process, we identified eight publications which met the eligibility criteria, with two being sub-group analyses [12,13] of one main study [14] (Fig. 1). A decision was made to include the six primary studies in this review and data from the subgroup analyses to provide additional information between adults and adolescents. There were no disagreements on the inclusion of the final studies among reviewers.

All studies included inhaled methoxyflurane at analgesic doses with a comparator being placebo or standard analgesia(s). Standard analgesia such as, Fentanyl, Morphine, Tramadol, Oxycodone, Ketamine, non-steroidal anti-inflammatory drugs (NSAID's) and Paracetamol as described in the six studies. Outcomes measured included improvement in pain scores, the patient-reported pain relief from the time of administration and up to 60 min after the time to first clinically significant pain

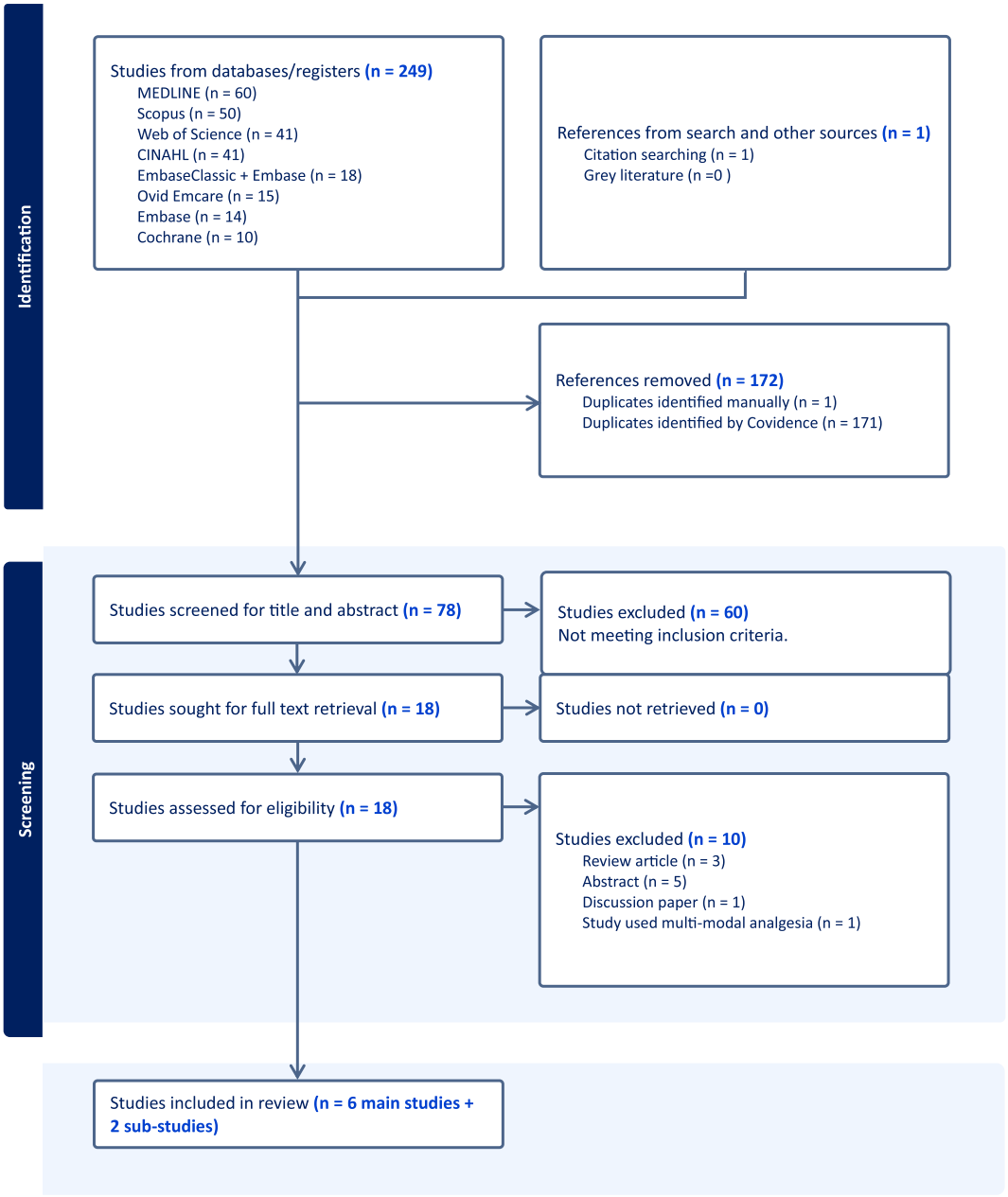

Fig. 1. PRISMA Study flowchart.

relief from the time of initial administration, the occurrence of adverse effects, and patient and staff satisfaction. Each study measured at least two investigated outcomes (Table 2).

3.1. GRADE quality of the evidence

The Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method for rating the quality of evidence rated, all six studies as high to moderate across the different outcomes. There were no serious study limitations that would warrant a further downgrade. Inconsistency in all six studies was minimal; the variance is found between studies that trialled Methoxyflurane versus placebo ($N = 1$) or Methoxyflurane versus standard analgesia ($N = 5$), and some studies did not capture the number of Methoxyflurane inhalations a patient self-administered [3,4,15-17]. All six included studies were rated overall at low risk for bias following the RoB 2.

3.2. Pain score improvements

Baseline pain scores were similar throughout all studies, ranging from around 63 mm to 66 mm. In four studies [3,4,15,16], participants recorded their pain intensity using the eleven-point Numeric Point Scale (NRS) (0 = no pain and 10 = unbearable pain). Most participants included voiced a Numeric Rating Scale (NRS) pain score of four to seven, except for two studies [4,15], which included patients with severe pain scores of NRS more than or equal to eight. The comparator was normal saline administered via a Penthrox inhaler in three studies [12-14] but was standard care analgesia in the other five studies, including the use of NSAIDs and opioids.

Analgesic efficacy was defined as a reduction in pain intensity from baseline, assessed by a Visual Analogue Scale (VAS) of 0-100 mm, where 0 = no pain and 100 = maximum pain. Studies also assessed the number of inhalations needed to obtain pain relief or patients requiring rescue medication (Table 4).

Generally, a reduction of at least 2 points on a 0–10 pain scale is considered clinically significant [18]. All six studies reported an improvement in pain scores for methoxyflurane compared to placebo or standard analgesics (Table 3). All participants had clinically significant pain relief at 10 min. The methoxyflurane group had an average improvement of 29.4 mm measured using the VAS pain scores, whereas the placebo group only had an improvement of 15.3 mm in pain scores.

The 5-min timepoint was the most used for pain score measurement among the included studies. Four studies showed significantly better pain reduction in the Methoxy group at this timepoint. Two studies recorded pain score at 20 min and three at 30 min. When the results are combined for these four studies [3,4,14,17] to assess for pain score reduction within 30 min, two of the studies [3,14] consistently reported significant better pain reduction in the methoxy group, while the other two studies [4,17] reported slight improvement in the comparator group.

Three studies [3,4,17] recorded pain scores at 60 min with two studies (3,4) reported better pain reduction in the methoxyflurane group. In the Wrong, 2022 study (17), while pain scores were significantly reduced in both groups over 60 min, the methoxyflurane group experienced statistically significant greater pain relief at 5 min compared to patients who were administered Ketorolac (p-value 0.041). No statistical significance was detected between groups at 15 and 30 mins. [7].

3.3. Inhalations needed / patients requiring 2nd inhalers or rescue medications

All studies reported a shorter time to obtain pain relief in the methoxyflurane group apart from one study [4] where patients had a Numerical Rating Scale (NRS) severe pain score of at least eight. Fewer participants in the methoxyflurane group also needed rescue medications. In the 2014 study by Coffey [14], almost 50 % of participants in the methoxyflurane group received pain relief with 1–5 inhalations, compared to 20.8 % in the placebo (inhaler) group. Only two patients from the methoxyflurane group required the use of rescue medications, as compared to 25 patients in the placebo group.

Data from the study and two sub-group analyses done in the United Kingdom [12-14] where percentages of participants obtaining pain relief were obtained, the numbers of participants obtaining pain relief within 1–5 inhalations were 2.39, 2.23 and 2.82 times higher respectively in the methoxyflurane group as compared to the comparator group (Table 4). Four studies utilised opioids including fentanyl and morphine as the comparator [3,4,15,16], while normal saline was used as a placebo in one study and two sub-group analyses [12-14] and NSAID were used in one study [17].

3.4. Patient and staff satisfaction

Brichko et al. [4] did not report on patient and staff satisfaction. For the other five studies, there was a higher proportion of patients and staff who were satisfied or very satisfied with methoxyflurane treatment compared to those who received the placebo (Table 4). From the five studies included, Borobia et al. in 2020 [3] assessed patient and clinician satisfaction with treatment (rating pain control, control of treatment administration, and adverse events) on the Numeric Rating Scale, in which 0 = not at all satisfied and 10 = completely satisfied. All other four studies and the fulfilment of patients' expectations in regard to pain control from the Borobia 2020 [3] study were assessed using a 5-point Likert qualitative scale (“Poor”, “Fair”, “Good”, “Very Good”, or “Excellent”).

Patients and clinicians in all six studies reported Very Good or Excellent satisfaction with methoxyflurane compared to the placebo group (Table 4). Although most patients voted “Good” or “Indifferent” in one study [12], most patients in the other four studies voted “Very Good” or “Satisfied”. For example, in Hartshorn 2019 [13] sub-group analysis, more than 95 % of patients, physicians, and nurses rated the methoxyflurane treatment as “Excellent”, “Very Good”, or “Good” compared with between 64 % and 68 % for placebo with normal Saline administered in a Penthrox inhaler.

3.5. Adverse effects

The evidence from all six randomized controlled trials (RCTs) in this review underscores the relative safety profile of methoxyflurane. Most studies reported minimal side effects, with the most frequently noted issues being transient sedation and mild nausea. These adverse effects were generally short-lived; in most instances, they did not lead to treatment discontinuation [3,4,12-17].

Serious adverse events were notably rare across the trials. Importantly, there were no instances of significant respiratory depression or hypotension, which are often associated with other analgesics [23,24]. The incidence of adverse effects was comparable to that observed with placebo or standard care, suggesting a favorable safety profile (see Table 5).

Regarding specific adverse effects, drowsiness and dizziness were reported in some cases, likely attributed to the rapid onset of methoxyflurane's action. However, these symptoms were typically self-limiting, resolving without intervention [3,4,12-17]. The studies provided additional reassurance about the absence of long-term effects, with one study reporting that clinical laboratory investigations showed no indications of nephrotoxicity or hepatotoxicity in participants monitored post-administration [14].

Table 2
Characteristics of included studies (Intervention = Inhaled methoxyflurane 3mls).

Study & setting	Inclusion Criteria	NRS Pain score for study entry at screening	Intervention	Comparator	Primary Outcome Measure time point	Secondary Outcome Measures	Risk of bias (RoB2)	Quality of Evidence (GRADE)
Coffey 2014: 6 EDs in UK	Age > 12 years Coffey 2016: 6 EDs in UK[a] Hartshorn 2019: 6 EDs in UK[a] Age > 18 years; Minor trauma including fractures, lacerations, burns, dislocations Age > 12 years and < 18 years with minor trauma	Moderate to severe pain scores of ≥4 to ≤7	Methoxyflurane inhaler as a single agent	Normal Saline 5 ml using a Penthrox® inhaler	Analgesic efficacy up to 20 min after administration of methoxyflurane	Occurrence of adverse effects Patient satisfaction Vital signs	Low	High
Mercadante 2019: 15 EDs in Italy	Age > 18 years; Trauma to single limb (fracture, dislocation, crushing, contusion)	≥ 4	Methoxyflurane inhaler as a single agent	NRS >7: Morphine 0.10 mg/kg; NRS >4: Paracetamol 1 g/Ketoprofen 100 mg IV	Analgesic efficacy up to 30 min after administration of methoxyflurane	Occurrence of adverse effects Patient satisfaction	Low	Moderate
Borobia 2020: 14 EDs in Spain	Conscious patients age 18 years or older with moderate to severe pain ≥ 4 on NRS	Moderate to severe pain scores of ≥4 to ≤7	Methoxyflurane inhaler as a single agent, a second inhaler was provided if required	NSAIDs for moderate and IV opioid and non-opioid analgesia for severe pain (only 9.4 % had opioids)	Analgesic efficacy up to 20 min after administration of methoxyflurane	Analgesic efficacy up to discharge after administration Occurrence of adverse effects Patient satisfaction Vital Signs Use of rescue medications	Low	Moderate
Brichko 2021: Tertiary ED Melbourne, Australia	Adults age 18–75 years;	Severe pain NRS ≥8	Methoxyflurane in addition to rescue analgesia up to 90 min from arrival	Paracetamol, NSAIDs, tramadol, oxycodone/ morphine	Analgesic efficacy up to 30 min after administration of methoxyflurane	Analgesic efficacy at different time points up to 90 min after administration of methoxyflurane	Low	Moderate
Wong 2022: Single ED in Hong Kong	Any musculoskeletal injury within 72 h of onset	Moderate pain 4–7 at screening	Methoxyflurane inhaler as a single agent	Ketorolac 30 mg IM	Analgesic efficacy up to 60 min after administration of methoxyflurane	Occurrence of adverse effects Patient satisfaction Vital signs	Low	Moderate
Iemsaengchairat, 2025; Single ED in Thailand	Age 18–60 years with acute anterior shoulder dislocation	NA	Methoxyflurane inhaler as a single agent	Midazolam 0.05 mg/kg and morphine 0.05 mg/kg.	Analgesic efficacy up to pre discharge, procedural time, pain score	Patient satisfaction and adverse effects	Low	Moderate

[a] Analysis of subgroups within Coffey 2014.

Table 3
Patient-reported pain reduction within 5–20 min and overall.

Study and no of participants		Baseline pain scores, mean (SD) VAS 0–100 mm NRS 0–10	5 mins	10 mins	15 mins	20 mins	Overall	*p* Value statistical and/or clinically significant
Coffey 2014	Methoxy ($n = 149$)	64.8 (VAS)	−23.1	−28.9	−34	−35	−30.2	Overall: <0.0001, and clinically significant
	Placebo (n = 149)	64.0 (VAS)	−11.3	−14.8	−15.5	−19	−15.2	N/A
Coffey 2016	Methoxy ($n = 103$)	66.2 (VAS)	−20.7	−27.4	−33.3	−34.8	−29	N/A
	Placebo ($n = 101$)	65.5 (VAS)	−8.0	−11.1	−12.3	−15.2	−11.6	N/A
Hartshorn 2019	Methoxy ($n = 48$)	61.7 (16.56) (VAS)	−24.5	−28.1	−31.6	−31.7	−29	N/A
	Placebo (n = 48)	61.0 (13.33) (VAS)	−14.6	−18.8	−19.2	−23.7	−19.1	N/A
Mercadante 2019	Methoxy ($n = 136$)	63.7 % (NRS 4–6) 36.3 % (NRS ≥ 7	−14.85[a]	−23.04[a]	N/A	N/A	−14.73[a]	*p*-value ≤0.05 for all time points
	Comparator ($n = 136$)	67.4 % moderate (NRS 4–6) 32.6 % severe (NRS ≥ 7)	−7.99	−15.8	N/A	N/A	−8.78	N/A
Borobia 2020	Methoxy ($n = 156$)	7.6 (1.39) (NRS)	−2.72[b]	−3.77[b]	−4.34	−4.94	-5.75 at 60 mins	N/A
	Comparator (n = 149)	7.5 (1.46) (NRS)	−1.04	−1.77	−2.46	−3.09	−4.92 at 60 mins	N/A
Brichko 2021	Methoxy ($n = 61$)	8.65 (NRS)	N/A	N/A	8 (17 % w relief)	7 at 30 m (−1.65) (25 % w relief)	30 % w relief at 60 mins	N/A
	Comparator ($n = 60$)	8.61 (NRS)	N/A	N/A	8 (5 % w relief)	8 at 30 m (−0.61) (9 % w relief)	10 % w relief at 60 mins	N/A
Wong 2022	Methoxy (n = 20)	65.3 (VAS)	−13.912[a]	N/A	−17.050	−22.715 at 30 mins	−30.392 at 60 mins	At 5 min: *p*-value 0.041
	Comparator (n = 20)	63.4 (VAS)	−4.888	N/A	−14.8	−24.035 at 30 mins	−31.958 at 60 mins	N/A
Iemsaengchairat 2025	Methoxy ($n = 25$)	9.92 (0.4) (VAS)	2.36	N/A	N/A	N/A	N/A	Baseline: p-value = 0.3 At 5 min: p-value =0.55 Not significant statistically
	Comparator (n = 25)	9.76 (0.66) (VAS)	2.48	N/A	N/A	N/A	N/A	

Comparator: detailed comparator information is included in Table 2.
N/A: Not available.
[a] Studies by Todd et al. in 1996 [19] and Gallagher et al. in 2001 [20] suggest a change of approximately 13 mm on a 100-mm visual analog scale (VAS) to be the minimum clinically important difference for acute pain.
[b] Clinically significant pain reduction using numeric pain rating scale NRS. Studies by Suzuki et al. in 2020 [21] suggest a change of ≥2 on a 11-point numeric pain rating scale (NRS) while Hirschfeld et al. in 2014 [22] suggest a change of one (1) point and 12.5 % should be considered clinically meaningful.

4. Discussion

Methoxyflurane has emerged as a popular analgesic agent for the management of acute traumatic pain in emergency settings. A thorough review of eight databases revealed six randomized controlled trials (RCTs) focused on its analgesic efficacy in EDs. These trials indicated that methoxyflurane provides rapid and effective pain relief for acute trauma, consistently outperforming placebo and standard analgesics. Results included significant reductions in pain scores and quicker onset of action, with high levels of satisfaction reported by both patients and treating clinicians [3,4,12-17].

Acute pain is a common occurrence in the ED. Pain assessment and analgesia administration within 30 min of arrival for patients with moderate to severe pain forms part of the Quality Standards for Australian EDs, the European Society of Emergency Medicine Guidelines, the American College of Emergency Physician (ACEP) guidelines and patient expectations. [25-27]

The effectiveness of methoxyflurane in acute traumatic pain management underscores its potential as a valuable analgesic option in emergency departments. The rapid onset of action and ease of administration make it particularly suitable for addressing the immediate needs of patients presenting with traumatic injuries [28]. Six randomized controlled trials evaluated methoxyflurane against placebo and standard therapies for managing acute traumatic pain. When compared to placebo, methoxyflurane consistently demonstrated effective analgesia, with a faster onset of pain relief occurring within 10 to 30 min after 6–10 inhalations. Additionally, when compared to standard analgesia, methoxyflurane also demonstrated superior pain relief, highlighting its efficacy in emergency department settings [3,4,12-17]. A single-center RCT conducted by Brickho et al. in 2021 [4] reported no significant difference in primary outcome or proportion of patients reporting at least a 50 % drop in pain scores at 30 min. However, a higher proportion of patients in the methoxyflurane arm reported a greater than 2-point drop in NRS pain scores and lower median pain scores at all time points compared to the standard therapy arm. Comparatively, traditional analgesic agents such as opioids and NSAIDs have shown similar reductions in pain scores but often with longer onset times and potential for adverse effects [3,4,16].

In a multi-centre randomized controlled trial conducted across 14 Spanish emergency departments, 70 % of patients in the standard analgesic treatment group received intravenous first-step analgesics, with 9.4 % of them treated with opioids. Methoxyflurane demonstrated a greater mean decrease in NRS pain intensity scores compared to standard analgesic treatment at all time points, showing a significant overall treatment difference up to 20 min. Additionally, the median time to first pain relief was significantly shorter with methoxyflurane (3 min) compared to standard analgesic treatment (10 min) [3]. Methoxyflurane can serve as a primary option, providing effective pain relief and potentially reducing opioid use and its associated risks, such as addiction and side effects.

Table 4
Inhalations needed to obtain pain relief/patients requiring rescue medication and adverse effects.

Study, country and participant number			1–5 inhalations No of participants (%)	6–10 inhalations No of participants (%)	>10 inhalations No of participants (%)	Pain relief within 1–10 inhalations and No relief No of patients (%)	Requesting 2nd inhaler /rescue meds No of participants (%)	Median time to first pain relief (methoxyflurane vs comparator)	Adverse effects[a]
	Methoxyflurane (n = 149)		74 (49.7)	52 (34.9)	–	126 (84.6)	2 (1.3) requesting rescue medications	4 min vs 10 mins	88 (59.10)[b] 2 (1.3)[c]
	Placebo - Normal (Saline via Penthrox inhaler) (n = 149)		31 (20.8)	45 (30.2)	–	76 (51)	25 (16.8) requesting rescue medications		61 (40.90)[b] 2 (1.3)[c]
Coffey 2014 UK	Coffey 2016 UK	Methoxyflurane (*n* = 102)	45 (44.1)	36 (35.3)	5 (4.9)	81 (79.4), 16 (15.7) no relief w/o rescue meds	25 (24.5) / 2 (2)	5 min vs 20 mins	43 (42.2)[b]
		Placebo - (Saline via Penthrox inhaler) (n = 101)	20 (19.8)	25 (24.8)	9 (8.9)	47 (46.5) no relief w/o rescue meds	15 (14.9) / 23 (22.8)		15 (14.9)[b]
	Hartshorn 2019 UK	Methoxyflurane (*n* = 47)	29 (62)	16 (34)	2 (4)	45 (95.7)	6 (12.8) / 2 (4.3)	1 min vs 3 mins	24 (51.1)[b]
		Placebo - (Saline via Penthrox inhaler) (n = 48)	11 (22.9)	20 (42)	8 (16)	31 (64.6) 9 (19) with no relief	9 (18.8) / 3 (6.3)		20 (41.7)[b]
Mercadante 2019 Italy	Methoxyflurane (n = 136)					N/A	3 (2.2)	9 min vs 15 min	23 (17)[b]
	Comparator (n = 136)					N/A	5 (3.7)		4 (3)[b]
Borobia 2020 Spain	Methoxyflurane (n = 156)		Not reported (These studies did not capture the number of inhalations a patient had. Some patients in the treatment arm may have had >10 inhalations).			N/A	8 (5.1)	3 min vs 10 mins	38 (24.4) reported 48 AEs[b] 2 (3.5)[c]
	Comparator: Standard Care (n = 149)					N/A	9 (18.8)		8 (5.4) reported 9 AEs[b]
Brichko 2021 Australia	Methoxyflurane (n = 61)					6 (10)	8 (5.1)	66 min (45–82)	0 reported
	Comparator: Standard analgesia (*n* = 60)					3 (5)	–	46 min (21–75)	0 reported
Wong 2022 Hong Kong	Methoxyflurane (*n* = 20)		N/A			N/A			7 (6 dizziness) [b]
	Comparator (*n* = 20)		N/A			N/A			0
Iemsaengchairat, 2025;	Methoxyflurane (*n* = 25)		N/A			N/A			3/23 (13 %) Drowsiness 2/23 (8.7 %) Dizziness
	Comparator (n = 25)		N/A			N/A			12/22 (54.54 %) Drowsiness 11/22 (50 %) Dizziness

N/A: Not available.
[a] Adverse events.
[b] Any treatment-emergent adverse event, most were mild.
[c] Severe treatment-emergent adverse event.

Table 5
Patient & staff satisfaction.

Study	Patient/Physician/Research Nurse		Treatment group	Poor / Very Unsatisfied	Fair / Unsatisfied	Good / Indifferent	Very Good / Satisfied	Excellent / Very Satisfied
Coffey 2016	Patient		Methoxy	12 (12.2 %)	10 (10.2 %)	34 (34.7 %)	22 (22.4 %)	20 (20.4 %)
			Placebo	43 (44.8 %)	23 (24 %)	20 (20.8 %)	6 (6.3 %)	4 (4.2 %)
	Physician		Methoxy	6 (10.9 %	8 (14.5 %)	25 (45.5 %)	10 (18.2 %)	6 (10.9 %)
			Placebo	20 (37 %)	20 (37 %)	10 (18.5 %)	4 (7.4 %)	0
	Research Nurse		Methoxy	15 (14.7 %)	13 (12.7 %)	35 (34.3 %)	20 (19.6 %)	19 (18.6 %)
			Placebo	53 (52.5 %)	22 (21.8 %)	18 (17.8 %)	6 (5.9 %)	2 (2 %)
	Hartshorn 2019	Patient	Methoxy ($n = 45$)	0	4	23	46	27
			Placebo (n = 47)	15	17	27	26	15
		Physician	Methoxy	0	5	21	44	30
			Placebo	22	13	32	26	7
		Research Nurse	Methoxy	2	2	21	38	2,36
			Placebo	18	16	36	17	18,11
Borobia 2020	Patient		Methoxy	Pain control 9/10, Comfort 9/10, Safety 9/10			77 % ($n = 152$)	
			Placebo	Pain control 7.75/10, Comfort 8/10, Safety 9/10			38 % ($n = 148$)	
	Clinician		Methoxy	N/A			72 % ($n = 147$)	
			Placebo	N/A			19 % ($n = 146$)	
Mercadante 2019	Patient		Methoxy	8.9 %	18.5 %	26.7 %	30.4 %	15.6 %
			Placebo	12 %	27.1 %	36.8 %	18 %	6 %
	Physician		Methoxy Placebo	Physicians' satisfactions were not assessed				
Wong 2022	Patient		Methoxy	0 %	5 %	35 %	40 %	20 %
			Ketorolac	10 %	5 %	30 %	35 %	20 %
Iemsaengchairat 2025	Patient		Methoxy Comparator	Satisfaction scores: 9.65 out of 10, SD:0.71 Satisfaction scores: 9.31 out of 10, SD 0.94				P-value 0.19

The six included RCTs reported common adverse effects, including dizziness, headache, and nausea, which were generally mild and transient. These effects are comparable to those seen with other inhalational analgesics and are generally well-tolerated by patients [3,4,12-14,16,17]. Although a higher incidence of adverse events was noted in the methoxyflurane groups compared to the placebo, these effects were consistent with the expected pharmacological responses for inhaled anaesthetics [13,29].

In evaluations of participant satisfaction, methoxyflurane groups consistently surpassed placebo and standard therapy groups in terms of pain control, comfort, and ease of use. In a subgroup analysis [13] of one RCT, Coffey et al. 2014 [14], participants rated their satisfaction with treatment arms —3mls methoxyflurane versus placebo as 5mls of normal saline —with >95 % of patients, physicians, and nurses reporting methoxyflurane treatment as "Excellent," "Very Good," or "Good," on the Likert 5-point scale compared to less than 68 % for the placebo groups, suggesting methoxyflurane to be a favorable choice of analgesic.

4.1. Treatment efficacy

Methoxyflurane is a volatile, halogenated anaesthetic known for its analgesic properties when administered in low doses via a hand-held inhalation device under trained supervision and is generally well tolerated [30]. Volatile anaesthetics are liquids stored at room temperature which require the use of a vaporiser for inhaled administration [23,29]. While methoxyflurane can be nephrotoxic at anaesthetic doses, there is a considerable volume of medical research suggesting there is no association with nephrotoxicity when administered at analgesic doses [23,31]. Additionally, methoxyflurane has been in use in Australia and New Zealand for over 40 years and more recently licenced for use in Europe, Latin America, and South Africa [27].

In our review, four studies have referred to Methoxyflurane's safety profile. However, they did not report any specific findings of nephrotoxicity or hepatotoxicity as they did not obtain serum lab samples [3,4,16,17]. Two of the included studies reported taking serum lab samples at baseline and 14 days of follow-up post-intervention, with results indicating no renal or hepatic injury to both the adult and adolescent groups [12,13]. However, it is worth noting that two studies that included serum lab results are sub-group analysis studies of Coffey et al., (2014) [14]. These two studies are Coffey et al. (2016) [12] focused on adult patients and Hartshorn et al. (2019), focused on Paediatric patients [13].

Methoxyflurane's effectiveness in treatment is driven by its capacity to rapidly alleviate pain without necessitating invasive procedures (such as intravenous cannulation) or extensive haemodynamic monitoring. All randomized controlled trials consistently attest to its efficacy in effectively addressing pain stemming from acute traumatic injuries such as fractures, burns, and lacerations, when compared to placebo or standard therapies such as NSAIDs. Further investigation into the comparative efficacy of methoxyflurane versus opioids for managing moderate-to-severe traumatic pain may yield valuable insights for developing acute pain protocols in ED settings.

4.2. Implications for practice

Effective management of acute traumatic pain entails numerous challenges, often compounded by constraints like limited time and resources. In ED, methoxyflurane offers an advantage as it can be quickly and easily administered, requiring minimal patient monitoring. This enables ED clinicians to allocate their time to other tasks while patients self-administer the medication under minimal supervision. Methoxyflurane proves particularly valuable for patients presenting with manageable traumatic injuries, such as dislocations and fractures, where severe pain might otherwise complicate treatment procedures. Its efficient administration potentially conserves resources and enhances overall patient experiences.

Inhaled analgesic methoxyflurane has several features that make it an attractive option as a choice of analgesic in ED, namely analgesic effect occurs within 5 min, comparable to the onset of both IV morphine and nitrous oxide, and more rapidly than the onset of intranasal fentanyl [32]. Methoxyflurane's method of delivery – via an inhalation device, quick onset, and ease of use (when supervised) may eliminate the necessity for intravenous access and various procedures involved in administering opioid drugs, thereby enhancing patient comfort and reducing the risk of adverse events.

The cost of methoxyflurane may appear to be higher compared to other analgesics used in ED, however it may be a cheaper option in the ED when other mitigating factors such as physician and nurses' time required for patients' pain management are considered. Further research into methoxyflurane's cost-effectiveness in ED settings is

recommended, especially given its potential impact on acute pain protocols amidst budget constraints in post-pandemic economies.

Overall, the evidence indicates that methoxyflurane is a safe and effective option for managing acute traumatic pain in emergency settings, with a favorable adverse effect profile that supports its clinical use. Its low incidence of adverse effects—comparable to placebo—highlights its suitability for pain management in acute situations.

5. Limitations

This systematic review has a few limitations. Firstly, our inclusion criteria restricted the review to studies published in English, which may introduce language bias and exclude relevant research published in other languages. Additionally, we focused exclusively on RCTs, which while offering high levels of evidence, often involve smaller sample sizes and varied comparators, potentially affecting the generalizability of the findings. Observational studies were not considered, which may have excluded valuable insights from broader real-world data. Furthermore, a significant proportion of the included studies lacked blinding or placebo control, which could introduce bias and impact the reliability of the results. These limitations should be considered when interpreting the conclusions of this review.

6. Conclusions

Methoxyflurane provides efficient, effective and safe pain relief for patients with acute traumatic pain in the Emergency Department. Patient and clinician satisfaction with analgesia, comfort and ease of administration surpasses standard analgesia. Adverse events are mild. It should be considered a suitable alternative option for the management of acute pain. Further research is required to evaluate its cost-effectiveness in the ED.

CRediT authorship contribution statement

Louisa Lam: Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Hendrika J. Brouwer:** Writing – review & editing, Writing – original draft, Methodology. **Meena Gupta:** Writing – review & editing, Writing – original draft, Methodology. **Chin Jin Ker:** Writing – review & editing, Writing – original draft, Data curation. **Conor Jones:** Writing – review & editing, Writing – original draft, Data curation. **Areeb Athar:** Writing – review & editing, Writing – original draft, Data curation. **Cristina Roman:** Writing – review & editing, Methodology. **Biswadev Mitra:** Writing – review & editing, Methodology. **Lisa Brichko:** Writing – review & editing. **Carl Luckhoff:** Writing – review & editing. **Natasha Jennings:** Writing – review & editing. **Peter Cameron:** Writing – review & editing, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajem.2025.04.021.

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