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Clinical assessment and risk stratification for prehospital use of methoxyflurane versus standard analgesia in adult patients with trauma pain

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Abstract:

Oligoanalgesia, the undertreatment of trauma-related pain using standard analgesics in prehospital and emergency departments, has been extensively documented as one of the major challenges affecting the effective treatment of trauma-related pain. When administered in low doses, methoxyflurane has been highlighted by numerous medical works of literature to provide an effective, nonopioid, nonnarcotic treatment alternative to standard analgesics for prehospital and emergency department use. Low-dose methoxyflurane has been associated with fast-pain relief in adult patients manifesting moderate-to-severe pain symptoms. This systematic review and meta-analysis aimed to assess the clinical implication of low-dose methoxyflurane use in prehospital and emergency departments in adult patients with moderate-to-severe trauma-related pain. Moreover, the review aimed at assessing the risk stratification associated with using low-dose methoxyflurane in prehospital and emergency departments. The systematic review and meta-analysis performed a comprehensive search for pertinent literature assessing the implications and risks of using low-dose methoxyflurane in adult patients exhibiting moderate-to-severe trauma-related pain in prehospital settings. A comparison between the use of low-dose methoxyflurane and standard-of-care analgesics, placebo, in prehospital settings was reported in four clinically conducted randomized controlled trials (RCTs). These RCTs included the STOP! trial, InMEDIATE, MEDIATA, and the PenASAP trials. A meta-analysis comparing the time taken to achieve first pain relief on initial treatment of patients with moderate-to-severe trauma-related pain favored the use of low-dose methoxyflurane to the standard-of-care analgesics (mean difference = −6.63, 95% confidence interval = −7.37, −5.09) on time taken to establish effective pain relief. Low-dose methoxyflurane has been associated with superior and faster pain relief in prehospital and emergency departments in adult patients exhibiting moderate-to-severe trauma-related pain compared to other standard analgesics.

Keywords:

Analgesic, emergency, methoxyflurane, prehospital, traumatic pain

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Introduction

Health-care researchers and personnel have extensively documented traumatic injuries as a global health crisis, with studies into the extent of damage accrued to traumatic injuries estimating over four and a half million fatalities annually and a significant number of physical and cognitive disabilities among the survivors.[1,2] Most studies investigating the etiology of acute pain highlight traumatic injuries as the major etiology of acute pain in prehospital and emergency department (ED) settings worldwide.[3-7] Galinski *et al*. and Mura *et al*. observed that most acute trauma patients in both prehospital and ED settings experience moderate-to-severe pain, with the majority of these cases witnessed in severely injured or high acuity trauma patients.[4-10]

According to the European Society for Emergency Medicine, despite numerous guidelines and recommendations that patients exhibiting trauma-associated pain should receive fast and effective analgesia in both prehospital and ED settings, many patients are still undertreated.[10-13] Undertreatment of trauma-related pain has been significantly associated with extended and prolonged hospital stays, unnecessary suffering, general dissatisfaction, increased susceptibility to psychological disorders such as depression, and reduced life quality among trauma patients.[14-16]

The analgesic treatments vary in their overall efficacy and mode of administration; thus, it can prove challenging for health-care providers to decide on the most suitable analgesia treatment to employ.[11] This observation comes into play, especially when some of the most commonly utilized analgesics have been proven to partly be associated with contributing factors to oligoanalgesia in patients with moderate-to-severe trauma pain.[17] Fabbri *et al*.[18] document some of the factors, leading to oligoanalgesia as; challenges in intravenous administration, logical constraints, possible side effects, weak analgesics, and elevated administrative burden associated with controlled drugs. Dißmann *et al*.[17] and Pierik *et al*.[19] highlight the failure to assess or underestimate the degree of pain by health-care providers and the lack of proper national or institutional guidelines for pain management as the major causes of oligoanalgesia among patients with moderate-to-severe trauma pain.

Currently, some of the most common mild-to-moderate traumatic pain management treatments include paracetamol, nonsteroid anti-inflammatory drugs (NSAIDs), and weak opioids. Stronger opioid analgesics are prescribed for moderate-to-severe traumatic pain.[20] Furthermore, nonopioid and multi-modal analgesic treatments, including sub-dissociative ketamine and nitrous oxide, have increased in popularity over the past decade.[21] The association of these treatments with several risk factors, including the risk of overdose for self-medicated paracetamol and NSAIDs, the risk of gastrointestinal disorders, nephropathy, cardiovascular disorders, and reduced healing of fractures accrued to the use of NSAIDs, and the intensive health resources needed for strong analgesic administration have warranted research into alternative treatment modalities for moderate-to-severe pain.

Methoxyflurane is a volatile, self-administered, rapid-acting, short-term inhalational analgesia. The analgesic is administered through a portable hand-held inhaler. Methoxyflurane is mainly self-administered in low doses, mostly 2–3 ml vials (a maximum of 15 ml weekly).[20] Self-administration of methoxyflurane allows the patient in moderate-to-severe pain to titrate the minimum effective dose required to achieve pain relief. Self-administration of methoxyflurane is done under strict medical supervision.

Methoxyflurane has become an attractive nonopioid alternative for moderate-to-severe pain medication in prehospital and ED settings based on several features. These features include methoxyflurane, a rapid-acting analgesic with pain relief accomplished with between 6–10 inhalations. Second, methoxyflurane ensures continuous pain relief with continuous use guaranteed for 25–30 min, with longer durations of pain relief achieved with more intermittent use of the analgesic. Thirdly, the occurrence of side effects is normally resolved on cessation of inhalation, and the side effects are documented to be mild and transient.[20] Low-dose methoxyflurane has not been associated with high-risk cardiovascular events nor respiratory depression on inhalation.[22] Finally, the Penthrox® inhaler is easy to use and store, compact, and allows the patients to control the level of analgesia they require studies investigating the overall distribution of methoxyflurane globally reveal that the use of low-dose methoxyflurane for short-term pain relief in prehospital and ED settings has been extensively used in the Australian and New Zealand health-care system for both adults and minors.[23-26] Currently, methoxyflurane use in the prehospital setting has been licensed in Europe, Canada, South Africa, Asian and Latin American countries, and the Gulf for use in adult patients exhibiting trauma-related pain. In Europe, the use of methoxyflurane has been reserved for conscious adult patients with moderate-to-severe trauma-related pain.[20]

The licensing of methoxyflurane use as emergency analgesia for adult patients suffering from moderate-to-severe trauma-related pain in these countries

has resulted from randomized controlled trials (RCTs) by health-care researchers. Critical data derived from the STOP! trial in Europe[23] and the InMEDIATE study in Spain shows patients' and healthcare professionals' high satisfaction rates. Moreover, the two studies showed a significant reduction in the overall visual analog pain scale (VAS) and shorter duration of pain relief achievement compared to standard analgesic medication in prehospital and ED settings.[18]

Therefore, based on the observable data from studies investigating the overall efficacy of methoxyflurane in prehospital and ED settings, we conducted a systematic review and meta-analysis with pertinent studies assessing the clinical outcomes and the risk factors associated with low-dose methoxyflurane use in prehospital and ED settings. The primary implication of this systematic review and meta-analysis was to provide ample evidence from the little literature exploring the use of methoxyflurane as an emergency analgesic to health-care professionals to aid in making informed treatment decisions.

Methods

Per the Preferred Report Items for Systematic Review and Meta-analysis (PRISMA) – 2020 guidelines, a population, Intervention, Comparison, and Outcomes strategy was assumed.

Population

The systematic review and meta-analysis included patients aged at least 18 years with trauma, defined as fractures, dislocation, crushing, or contusion, and exhibiting an above four NHS pain score. The patients had to be rescued from a prehospital environment or presented at a hospital emergency department. The patients had to achieve medical stability, alertness, and collaboration with their ability to communicate and not interfere in any way.

Intervention

Low-dose methoxyflurane was administered with a single-handed inhaler containing 3 ml of methoxyflurane. The administration of the methoxyflurane vapor had to be self-administered under medical supervision, with effective administration achieved when the liquid vaporized and was inhaled through the inhaler's mouthpiece.

Comparison

Standard analgesia was the primarily used placebo comparison to methoxyflurane. Standard analgesic treatments included paracetamol, NSAIDs, and weak and strong opioids. No treatment at all was also enlisted as a potential comparator.

Outcome

The major primary outcome assessed by the systematic review and meta-analysis was the patients' duration and intensity of pain. Secondary outcome measures investigated included treatment satisfaction and the risk of adverse effects.

Search strategy

The Cochrane Database of Systematic Reviews, EMBASE, PubMed, and Web of Science medical databases searched for RCTs. There was an electronic search for any active clinical trials on the topic. Other potential studies were also found using the Google Scholar Search engine. Manually searching references from peer-reviewed journals were also done.

Keywords dictated the search approach. To extract literature from 2010 to 2022, a search method using the English language and chronological filters were used. The following search terms were used to generate eligible literature; methoxyflurane OR Penthrox AND analgesic OR standard analgesia, AND clinical assessment AND risk stratification.

Inclusion and exclusion criteria

Studies with abstracts and articles included in this systematic review had to adhere to the following inclusion criteria:

1. Studies that reported risk estimates
2. Studies reporting novel research results or prospective RCTs
3. Studies dating from the year 2010 onward. To provide comprehensive and updated findings, the review found it paramount to include the most recently published data on the application of methoxyflurane in clinical and emergency department settings
4. Studies with patients exhibiting moderate-to-severe trauma-related pain
5. Studies in the English language
6. Studies of patients above 18 years.

Study selection and data analysis

The systematic review was carried out by two researchers (HZ and AE). The database was used in conjunction with the above criteria to decide which summaries to include and which to ignore. In cases where the primary author's information could not be obtained, the researcher independently confirmed the inconsistencies. Each researcher selected and reviewed the full-length articles accepted for consideration. After a consensus was reached, any conflicts that arose were analyzed and resolved to provide data with the highest degree of transparency possible.

Data from an extensive search of medical databases for appropriate criteria were tabulated in the study

description. The results of each study are also included in the table, and each feature of the individual study is shown.

Based on the worthwhile statistical data from the literature analysis, the review conducted a meta-analysis on the research question. For this purpose, the review adopted the Cochrane Handbook for Systematic reviews. Specifically, a statistical appraisal was performed using the review manager (RevMan) software Version 5.4) ClickTime Inc, San Francisco, CA, US) as per the Cochrane guidance for conducting systematic reviews. Thel-squared (I^2) test was administered for the assessment of the overall heterogeneity based on recommendations from the Cochrane Handbook for Systematic Reviews of interventions with 0%–40% might not be important, 30%–60% may represent moderate heterogeneity, 50%–90% may represent substantial heterogeneity, 75%–100% considerable heterogeneity. The importance of the observed value of I2 depends on the magnitude and direction of effects and the strength of evidence for heterogeneity (e.g. *P* value from the Chi-squared test, or a confidence interval (CI) for I^2).

Statistical analysis was performed using RevMan 5.4 software. Risk ratio (RR)/odds ratio was used for outcome estimation whenever appropriate with 95% CI. The fixed/random-effects model was used according to heterogeneities.

Hidden randomization, specified inclusion and exclusion parameters, blinded study, individual screening, blinded data processing, and intentions to treat were used to reduce bias. Health workers providing treatments could not be blinded. The overall risk of bias in studies was assessed using the Cochrane Handbook Tool for Risk of Bias. Based on the PRISMA 2020 guidelines for conducting systematic reviews and meta-analyses, the review employed the Cochrane risk-of-bias tool for randomized trials, version 2.0 (RoB 2), to assess bias in the RCTs included in this systematic review and meta-analysis. The REVMAN 5.4 software was utilized in creating the summary for risk of bias, as presented in Figure 1. The risk of bias for studies was defined as high, low, or uncertain risk of bias. Figure 1 represents data from sequencing, allocation concealment, blinding of participants, staff, and outcome evaluators, incomplete data, selective results reporting, and other risks, including the risk of overall summary bias.

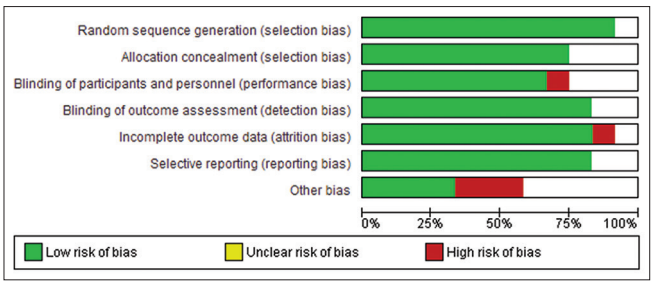

Figure 1: Summary bias risk reported in the RCTs. RCTs: Randomized controlled trials

Results

On running the previously mentioned search terms on various digital medical databases, the systematic review and meta-analysis uncovered fifty potential studies for inclusion in the review. Initial screening of these articles and publications by the researchers led to the exclusion of thirty studies for being duplicates. Twenty studies proceeded for full-text review, where Sixteen studies were excluded as per the eligibility criteria derived above. The key reasons for exclusion included the retrospective nature of the studies, studies performed on minors under eighteen, studies where the risk estimates were not reported, nonrandomized trials, and studies not in the English language. Thus, the systematic review and meta-analysis uncovered four randomized controlled studies for inclusion in the review. The literature search results were then represented in a PRISMA flowchart in Figure 2. The four studies included in the systematic review and meta-analysis described extensively RCTs on the use of methoxyflurane for trauma-related pain in adult patients. The results of these studies are summarized in Table 1. These RCTs included STOP!;[27,28] InMEDIATE;[29] MEDITA;[30] and PenASAP.[31] Since the PenASAP RCT did not indicate any determinable results despite its relevance, the systematic review and meta-analysis found it most suitable to exclude the study from the resultant meta-analysis.

The STOP! trial registered under the clinical trials databases as (NCT01420159) was a double-blinded, multicentered, randomized study conducted in the United Kingdom to compare the effects of low-dose methoxyflurane with placebo in adult patients with acute minor trauma in the United Kingdom emergency departments.[27,28] The study enrolled 300 participants, 90 of whom were adolescents, leading to their expulsion from the study. Results of 204 adults were then published, with the measured primary outcome being a change in pain intensity from baseline to 20 min after initial inhalation.

The open-labeled, randomized InMEDIATE study registered as clinical trial number NCT03256903 was conducted in the Spanish prehospital and ED settings to compare low-dose methoxyflurane and standard analgesia in adult patients with moderate-to-severe trauma-related pain. The study recorded outcomes regarding the change in co-primary endpoints from

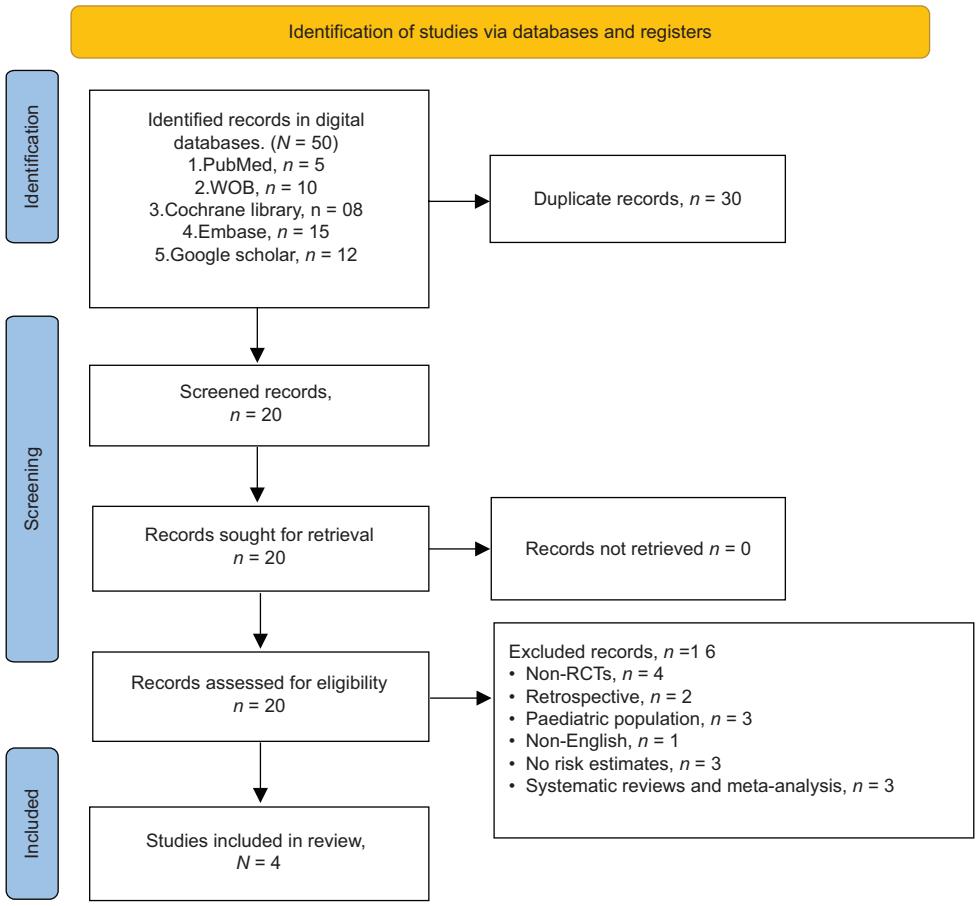

Figure 2: PRISMA Flow chart. PRISMA: Preferred Report Items for Systematic Review and Meta-analysis

Table 1: The results of the studies

Study	Intervention (population)	Primary outcome	Adverse effects.	Other outcomes
STOP![27,28]	Methoxyflurane, *n*=103 Placebo, *n*=101	Changes in pain intensity at 5, ten, 15, and 20 minutes after the first treatment. Overall change, *n*=−17.4 mm (95% CI, −22.3-−12.5): *P*<0.0001	Methoxyflurane, *n*=65 Placebo, *n*=41	Median time to first pain relief; 1. Methoxyflurane, *n*=5 min 2. Placebo, *n*=20 min
InMEDIATE[29]	Methoxyflurane, *n*=156 Placebo, *n*=149	Change in pain intensity after 20 min. Overall difference, 1.00 (95% CI, 0.84-1.32)	Methoxyflurane, *n*=38 Placebo, *n*=8	Median time to pain relief, 1. Methoxyflurane, *n*=3 min 2. Placebo, *n*=10 min
MEDITA[30]	Methoxyflurane, *n*=135 Placebo, *n*=135	Changes in pain intensity after 10 min. Overall change, −5.94 (95% CI=−8.83-−3.06) *P*<0.005	Methoxyflurane, *n*=23 Placebo, *n*=4	Median time to pain relief, 1. Methoxyflurane, *n*=9 min 2. Placebo, *n*=15 min
PenASAP[31]	Methoxyflurane, *n*=178 Placebo, *n*=173	Changes in pain intensity, 9.2 (95% CI=5.3–13.1) *P*<0.0001	Methoxyflurane, *n*=87 Placebo, *n*=21	Median time to pain relief, 1. Methoxyflurane, *n*=35 min 2. Placebo, *n*=Not achieved

CI: Confidence interval

baseline and the duration of time taken to achieve first pain relief.[29]

The MEDITA trial (NCT03585374) was similar to the InMEDIATE trial in its open-labeled, randomized approach, comparing low-dose methoxyflurane with standard care and the primary outcomes measurement of changes in pain intensity from baseline.[30] The MEDITA trial was conducted in Italian hospital prehospital and ED settings. Moreover, the changes in pain intensity from baseline were measured to the 10th min after initial treatment.

Similarly, the PenASAP study (NCT03798899) compared low-dose methoxyflurane with standard-of-care interventions in the French prehospital and ED settings among patients suffering from moderate-to-severe

trauma-associated pain.[31] The study's primary outcome was the duration taken to achieve pain relief with the treatment intervention topped up with a standard-of-care analgesics.

Overall, the four studies enrolled a total of one thousand two hundred and ten patients. Initial assessment by the researchers excluded 96 patients in the STOP! trial as their ages were less than eighteen and they belonged to the pediatric population. Further stratification of patient data and conditions led to the exclusion of 24 patients with Visual Analog pain Scale ratings below 30 ml. This observation was accredited to administering standard-of-care medications before or during the 1st min of methoxyflurane inhalation. Therefore, only 1090 patients were included in the meta-analytical decomposition. The demographic characteristics and treatment responses of the patients are summarized in Table 2.

The time taken to relieve the pain was significantly shorter with low-dose methoxyflurane than with placebo. The median time required to achieve pain relief among patients receiving low-dose methoxyflurane was 10 min compared to 18 min in the placebo group (hazard ratio = 2.03, 95% CI, 1.75–2.36). Figure 3 shows the estimated time to first pain relief in patients treated with low-dose methoxyflurane. The majority of data included in this systematic review and meta-analysis calculated the time taken to arrive at a desired pain relief state in terms of different periods measuring from initial inhalation, 3, 5, 10, 15, and 20 min after the first inhalation. Due to the heterogeneity witnessed in the variations of pain relief measurement, the review decided to calculate the overall mean and standard deviation of the reported estimated time taken to achieve pain relief. A meta-analysis of this data found that low-dose methoxyflurane was associated with shorter periods of pain relief compared to placebo (MD, mean difference = −6.63, 95% CI, −7.37, −5.09). Moreover, most of the studies included in this systematic review and meta-analysis compared the standard-of-care analgesics and low-dose methoxyflurane in terms of patients' and healthcare workers' administering perspectives of usability, efficacy, and practicality. Most patients and health-care workers examined by the study were "satisfied" or "very satisfied" with low-dose methoxyflurane as emergency analgesia. This observation was seen in 64% of the sample population compared to 49%.

The incidence of adverse effects was generally low between the two groups (RR = 2.04, 95% CI, 1.54–2.69) $P < 0.00001$. These results were further collaborated by the fact that there was no reported treatment drop-out during the trial period. However, low-dose methoxyflurane was significantly associated with the prevalence of dizziness, headaches, somnolence, and drunk sensations in the sample population. One percent of the sample population reported severe adverse effects from using low-dose methoxyflurane. Figure 4 shows the prevalence of adverse events in patients treated with methoxyflurane.

Discussion

The main aim of this systematic review and meta-analysis was to assess the clinical implications and the potential risks accrued to the use of low-dose methoxyflurane in prehospital and ED settings. From the results derived

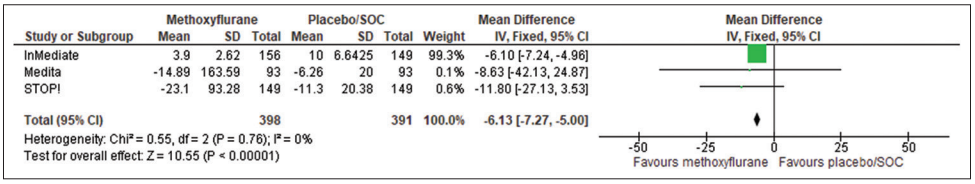

Figure 3: Forest plot showing the estimated time for first pain relief among patients treated with low-dose methoxyflurane

Table 2: The demographic characteristics and treatment responses of the patients

	Intervention (population, *n*)					
	Methoxyflurane (*n*=536)	Placebo/standard of care				
		No treatment (*n*=256)	Paracetamol (*n*=115)	NSAID (*n*=127)	Opioids (*n*=56)	Total (*n*=554)
Age (mean)	43.3 (17.9)	36.7 (15.4)	45.2 (18.3)	44.0 (17.6)	56.8 (19.1)	42.7 (17.9)
Sex						
Male	288 (53.7)	141 (55.1)	61 (53.0)	73 (57.5)	18 (32.1)	293 (52.9)
Female	248 (46.3)	115 (44.9)	54 (47.0)	54 (42.5)	38 (67.9)	261 (47.1)
Mean VAS score at randomization (SD)	67.6 (15.5)	65.0 (13.5)	59.5 (13.7)	73.9 (15.0)	81.4 (10.3)	67.6 (15.1)
Mean VAS scores at initial treatment (SD)	69.5 (16.2)	67.4 (15.5)	63.8 (16.1)	74.3 (14.5)	79.1 (13.7)	69.4 (16.0)

SD: Standard deviation, NSAID: Nonsteroid anti-inflammatory drug, VAS: Visual analog scale

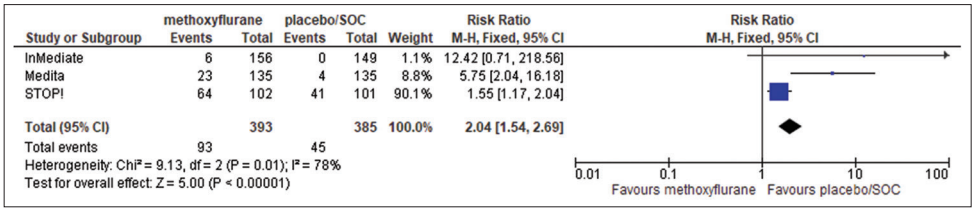

Figure 4: Forest plot showing the prevalence of adverse effects in patients treated with methoxyflurane

in this review, we find that low-dose methoxyflurane, compared to other standard-of-care (SOC) analgesics, is associated with higher efficacy in adult patients with trauma-related pain. In prehospital and ED settings, low-dose methoxyflurane demonstrates its higher superiority to other emergency care analgesics because of the significantly shorter time needed to achieve pain relief in adult trauma-related patients.

Despite the heterogeneity in the measurements of durations taken to achieve initial pain relief, this systematic review and meta-analysis observed that the most significant change in the Visual Analog Scale in terms of pain was observed during the first 5 min after self-administration of the low-dose methoxyflurane. As documented by most studies, these changes in pain intensity occurred consistently throughout the first 30 min after initiating treatment.[27-29,32] A majority of studies included in his systematic review and meta-analysis utilized a single, 3 ml vial of low dose methoxyflurane which in approximation ensured a 25–60 min pain relief effect, which significantly depended on the frequency of inhalation[33] Administering a second vial to ensure longer pain relief could be used in clinical practice. Moreover, in the clinical assessment of the use of low-dose methoxyflurane, patient and health worker populations' perspectives on the documented efficacy and utility of the analgesic for prehospital and ED settings. This review and meta-analysis observe that most patients and health care professionals expressed significantly high levels of satisfaction with using low-dose methoxyflurane compared to other standard analgesic treatments used in prehospital and emergency departments. This observation in increased satisfaction scores for patients and health care workers has been directly associated with the differences in the modes of administration of emergency analgesics. They observed that the duration taken for randomization and the onset of pain relief from methoxyflurane and standard-of-care analgesics had a 6-min differential. The study accrues this finding to the differences observed in the administration routes of the two groups with standard-of-care analgesics administered intravenously, which has been associated with extended analgesia administration time and the onset of pain relief in prehospital and ED settings[30] This observation was also reported in the InMEDIATE trial and the STOP! Trial showed 7- and 4-min differentials in the median time to the onset of pain relief.[27-29] Given the primary need to intervene as quickly as possible to relieve the patient's pain while undertaking diagnostic therapy processes, the superior efficacy of administration of low-dose methoxyflurane compared to other emergency analgesia has been witnessed in the significantly shorter median time to the onset of pain relief in adult patients seeking prehospital help for trauma-related pain. According to Borobia *et al*., the median time needed for the onset of pain relief from the initiation of treatment was significantly shorter for the methoxyflurane group compared to the placebo. This observation showed that the quicker onset of action of methoxyflurane was not constrained to the differences taken to administer the intervention, with the study citing the superior efficacy of methoxyflurane.[29]

This systematic review and meta-analysis on the clinical implications and risk stratification of low-dose methoxyflurane as an effective treatment option for prehospital adult patients with moderate-to-severe trauma pain revealed a higher satisfaction and rating score due to numerous advantages accrued to low-dose-methoxyflurane. These advantages include the relative ease of preparing and administering methoxyflurane, self-administration, and self-control of levels of methoxyflurane have been significantly associated with a decrease in the care burden in prehospital and ED settings. Moreover, the reported elevated levels of effectiveness as a short-term treatment option for moderate-to-severe trauma-related pain of methoxyflurane has also been the predominant advantage accrued to low-dose methoxyflurane.[27-31]

According to an analysis conducted by Casamayor *et al*., methoxyflurane has been associated with low physiological monitoring needs compared to other analgesics, such as opioid analgesics.[34] The elimination of administrative costs due to intravenous administration of other analgesic treatments and increased labor costs in medical departments is also an advantage accrued to using methoxyflurane compared to other analgesics. The administration of low-dose methoxyflurane has also been associated with decreased stress levels compared to other trauma-related pain treatment interventions such as morphine. More practicability in an out-of-hospital

contest has been a key advocate point for using low-dose methoxyflurane in prehospital and ED contexts.

With most of the global health-care population opting for more noninvasive and nonnarcotic analgesia with rapid-acting potency, nitrous oxide and methoxyflurane have become significant players in emergency settings. In comparative studies assessing the clinical implications of methoxyflurane and nitrous oxide (50:50 oxygen), Nitrous oxide was the most effective analgesic with a significantly quick onset of action, rapid reversibility, and few reported side effects.[35] However, Nitrous oxide gas canisters proved to be cumbersome and impractical in out-of-hospital settings, and the need for extra care when used in patients with trapped air whereby expansion would be dangerous.[35-37]

Historically, methoxyflurane use was significantly associated with nephrotoxicity, as reported in patients subjected to high doses due to deep methoxyflurane anesthesia.[38] Cousins *et al*.[39] and Coffrey *et al*.[28] attribute renal failure to the metabolism of methoxyflurane in the kidney and liver, releasing fluoride ions. However, recent research into low doses of methoxyflurane use as clinical analgesia does not associate these low doses of methoxyflurane with adverse renal effects.[40] Furthermore, using a prescribed Penthrox inhaler carrying 6 ml per day and 15 ml per week presents a larger safety margin for using methoxyflurane as an analgesic.

The prevalence of adverse effects in the methoxyflurane treatment group was significantly more than in the placebo/SOC group (RR = 2.04, 95% CI, 1.54–2.69). However, these adverse effects were mostly minor and transient, with few or no treatment discontinuation reported in the majority of included studies in this review. Despite, the InMEDIATE, MEDIATA PenASAP and the STOP! Trials reporting a significant prevalence of adverse effects, a higher patient acceptance of treatment, and higher median ratings on the efficacy scores showed that low doses of methoxyflurane are an effective treatment alternative for prehospital and ED settings for adults with trauma-related pain.

Limitations

This systematic review and meta-analysis report several challenges experienced while undertaking this research. First, limitations in the amount of pertinent literature and randomized clinical trials around the use of low-dose methoxyflurane in prehospital and ED settings across the globe proved a major challenge, with the study only assessing four. Second, most of the included studies were concentrated in the European region, mainly Spain, Italy, the United Kingdom, and France. Hence, the assessment of the clinical implication of low-dose methoxyflurane in prehospital and ED settings across the globe was highly limited. Third, the review found no randomized trials conducted in exclusive prehospital settings, with the majority of included studies reporting the use of methoxyflurane in either prehospital and ED settings or exclusively emergency department data. Finally, the variations in the types of randomized controlled studies in terms of study designs and the interpretation and measurements of pain scores and durations for the onset of pain relief posed a challenge in the effective interpretation of data.

Conclusions

Methoxyflurane, in low doses, provides a superior, more effective, and rapid pain relief in adult patients with trauma-related pain in prehospital and emergency room settings. These findings are consistent with results obtained from a similar systematic review and meta-analysis conducted by Fabbri *et al*. in 2021 and a nonrandomized clinical trial conducted by Smith *et al*. in 2022 in the United Kingdom healthcare sector. Low-dose inhaled methoxyflurane characteristics such as easy portability, noninvasive, nonnarcotic, ease of use, and self-administration have significantly increased its adoption in prehospital and emergency departments for patients with moderate-to-severe trauma-related pain.

Moreover, low-dose methoxyflurane is significantly tolerable compared to other standard analgesics used in prehospital and ED settings for adult patients experiencing moderate-to-severe trauma pain. Low-dose methoxyflurane has also been associated with minimal supervision and eliminating intravenous administration tools, cutting back high emergency costs. This systematic review and meta-analysis recommend that patients be thoroughly coached on using the Penthrox inhaler. Furthermore, further studies are required to compare methoxyflurane with other analgesic modalities to provide a wide array of pertinent data for clinicians on the appropriate use of methoxyflurane in emergency medicine.

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Author contributions statement

Zaki Hany, Bashir Khalid, Elmoheen Amr, Shaban Eman, Iftikhar Haris; Conceptualization – Data curation – Formal analysis – Investigation – Methodology.

Zaki Hany, Turkmen Suha, Azad Aftab, Shaban Eman, Iftikhar Haris, Shallik Nabil; Software – Supervision – Validation – Visualization – Writing – original draft – Writing –review and editing.

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None declared.

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