Comparison of inhalational methoxyflurane, intranasal fentanyl, and intravenous morphine for treatment of prehospital acute pain in Norway (PreMeFen): a randomised, non-inferiority, three-arm, phase 3 trial

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Summary

Background Adequate pain control is essential; however, acute pain is often undertreated in prehospital care. This study aimed to evaluate three analgesic regimens for treating acute pain in an ambulance setting.

Methods PreMeFen is a randomised, open-label, non-inferiority, three-arm, phase 3 trial conducted in the working areas of the ground ambulance service of the Innlandet Hospital Trust, Norway. Patients aged 18–69 years and 70 years and older with traumatic or medical acute pain scoring 4 or higher on the Numeric Rating Scale (NRS) were randomly assigned (1:1:1) to receive in titration doses 3 mL inhalational methoxyflurane, 50 µg or 100 µg intranasal fentanyl, or 0·05 mg/kg or 0·1 mg/kg intravenous morphine, respectively, depending on the age group. The primary endpoint was change in pain NRS score from baseline to 10 min after treatment start and was analysed per protocol. The non-inferiority margin was 1·3. This trial is registered with ClinicalTrials.gov (NCT05137184) and is completed.

Findings Between Nov 12, 2021, and April 22, 2023, 632 patients were assessed for eligibility, and 338 were randomly assigned to methoxyflurane (n=112), fentanyl (n=115), or morphine (n=111). 281 patients were included in the per-protocol population. 145 (52%) of 281 patients were female and 136 (48%) were male. Median age was 61 years (IQR 47–75). The baseline NRS score was 7·6 (SD 1·8). Mean NRS score changes after 10 min were –3·31 (SD 2·67) for methoxyflurane, –1·98 (2·28) for fentanyl, and –2·74 (2·12) for morphine. Comparing changes in mean NRS score while adjusting for baseline showed that methoxyflurane was non-inferior to fentanyl (–1·33 [95% CI –2·01 to –0·64]) and morphine (–0·36 [–1·03 to 0·31]). Intranasal fentanyl was not non-inferior to morphine at 10 min (0·91 [0·27 to 1·55]). Adverse events occurred in 26 (24%) of 109 patients in the morphine group, 27 (24%) of 112 in the fentanyl group, and 24 (22%) of 111 in the methoxyflurane group. Two serious adverse events, respiratory depression (grade 2) and loss of consciousness (grade 3), occurred in the same patient in the methoxyflurane group. There were no treatment-related deaths.

Interpretation Inhalational methoxyflurane is non-inferior to intranasal fentanyl and intravenous morphine for acute pain management in the prehospital environment, assessed 10 min after administration. Inhalational methoxyflurane serves as a valuable non-intravenous alternative in the early phase of treatment and might bridge the gap to longer-acting analgesics.

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Introduction

Pain is frequently encountered among patients receiving treatment from emergency medical service personnel, with reports of up to 53% of patients having moderate to severe pain.[1] Inadequate prehospital treatment of pain is widespread and well documented,[2,3] and it can have immediate and long-term consequences.[4] Undertreatment of pain and variability in pain management strategies mirror the differences in competencies among prehospital personnel, ranging from technicians with basic training to experienced physicians.[5,6] The prehospital setting also adds challenges to pain management, including weather, low temperatures, and poor access to the patient.[7] Nevertheless, the International Association for the Study of Pain emphasised in the Declaration of Montreal that pain management is a health challenge and defined access to pain relief as a human right.[8,9]

Traditionally, prehospital pain management has mainly involved intravenous opioid administration. However, peripheral venous cannulation has been reported to be unsuccessful in 12–26% of adults,[10] resulting in oligoanalgesia. Patients might accordingly benefit from alternative, non-intravenous analgesic administration routes that are safe, effective, easy to administer, and fast-acting. Two such alternative

Research in context

Evidence before this study

We searched PubMed with the search terms ("fentanyl" OR "methoxyflurane") AND ("intranasal" OR "inhalation") AND ("emergency department" OR "emergency medical services" OR "ambulance" OR "air ambulance" OR "prehospital" OR "pre-hospital") AND ("acute pain" OR "pain management" OR "pain treatment" OR "pain therapy" OR "analgesia") for studies published between June 1, 2006, and June 1, 2021, later updated to June 1, 2025. We focused on clinical studies, clinical trials, randomised controlled trials, reviews, systematic reviews, and meta-analyses. A systematic review indicated that intranasal fentanyl and intravenous morphine have similar analgesic effects, as measured by changes in the Numeric Rating Scale, within pre-hospital settings. However, the quality of evidence was low, and studies did not assess time-to-effect. Methoxyflurane has shown significantly inferior analgesic efficacy compared with opioids at typical doses, but due to its rapid onset of action it might be valuable for immediate pain management when intravenous access is challenging. A large retrospective analysis showed that intranasal fentanyl and intravenous morphine were more efficacious than methoxyflurane, with no difference between fentanyl and morphine, but time-to-effect again was not assessed. Therefore, robust evidence comparing methoxyflurane, intranasal fentanyl, and intravenous morphine for immediate pain relief in prehospital care is scarce, and no clinical trial has directly performed this comparison.

Added value of this study

The PreMeFen study contributes to the literature by establishing that methoxyflurane is non-inferior to intravenous morphine and intranasal fentanyl in the management of acute, moderate to severe traumatic and non-traumatic pain within the prehospital context, as assessed 10 min post-administration. Notably, while intranasal fentanyl did not show non-inferiority to intravenous morphine at 10 min, it was shown to be non-inferior at 20 min and 30 min. This study adds to existing evidence of non-intravenous alternatives for immediate pain relief in prehospital settings, offering real-world insights into analgesic regimens pertinent to ambulance and emergency care environments. To our knowledge, this study represents the first randomised trial comparing these three treatment regimens.

Implications of all the available evidence

Methoxyflurane and intranasal fentanyl are non-intravenous alternatives to morphine, which are available and show effectiveness for prompt pain relief in prehospital scenarios, with few serious adverse events. Our findings suggest that methoxyflurane serves as a useful non-intravenous alternative in the initial phase in which immediate pain relief is crucial and intravenous access remains unestablished. Furthermore, it acts as a bridge to longer-acting analgesics. Intranasal fentanyl necessitates a longer time frame to achieve its analgesic effect, establishing its non-inferiority to intravenous morphine after 20 min.

administrations are the intranasal and inhalational routes. Intranasal fentanyl is a highly potent, synthetic lipophilic opioid,[11,12] whereas inhalational methoxyflurane is a non-narcotic, volatile anaesthetic often administered in low doses and inhaled through a specialised inhaler.[3,13] Intranasal fentanyl is approved for breakthrough cancer-related pain,[14] and has been introduced for prehospital acute pain.[15] Methoxyflurane is widely used in prehospital settings in Australia and New Zealand, but to a lesser extent in Europe.[16] Although equipotency studies indicate a modest effect compared with intravenous fentanyl,[17] we have shown feasibility and good patient satisfaction of prehospital methoxyflurane administrated for ski-related injuries in an alpine environment.[7] However, systematic reviews suggest the need for prehospital studies to establish efficacy and safety for these alternatives in the prehospital treatment of acute pain.[18–20] We aimed to compare two non-intravenous alternatives, methoxyflurane and intranasal fentanyl, with each other and with the established standard of intravenous morphine.

See Online for appendix

The objective was to establish whether non-intravenous methoxyflurane and intranasal fentanyl were as effective as intravenous morphine for initial pain treatment for a broad spectrum of painful conditions performed by paramedics in real prehospital acute settings.

Methods

Study design and participants

The PreMeFen study is a randomised, three-arm, open-label, single-centre, non-inferiority, phase 3 clinical trial conducted in three rural and urban areas of the ground ambulance service of Innlandet Hospital Trust, Norway. The study was performed in line with the published study protocol,[21] and according to the principles of the Helsinki Declaration.[22]

Patients aged 18 years or older with medical or traumatic acute moderate to severe pain scoring 4 or higher on the Numeric Rating Scale (NRS) were eligible. Inclusion criteria also included normal physiology and ability to provide informed consent. Exclusion criteria included life-threatening or limb-threatening conditions, head injuries with neurological impairment, and allergies to the treatment medications (appendix p 5). Ambulance personnel assessed inclusion during the primary medical examination and obtained oral consent before inclusion and randomisation. Patients were treated on-site and enroute to hospital. End of study was when the patients were handed over to either the emergency department, emergency outpatient clinic, general practitioner, or when left on scene, depending on the patient's condition.

Oral patient consent was obtained, witnessed by the two ambulance personnel on scene and documented in

the case report form (appendix p 2). All patients received written information about the study, including details on how to withdraw from participation. Follow-up phone calls were attempted 2 weeks after inclusion for all participants. The consent procedure was in line with Norwegian regulations. The study protocol and consent documents were approved by the Regional Committees for Medical Research Ethics, South-East, Norway (255159) and the Norwegian Medicines Agency (EudraCT Number 2021-000549-42). The CONSORT checklist for randomised controlled trials was used with the extension for non-inferiority trials (appendix pp 3–4). The trial was registered with ClinicalTrials.gov (NCT05137184) and is complete.

Randomisation and masking

Patients were randomly assigned (1:1:1) to inhalational methoxyflurane, intranasal fentanyl, or intravenous morphine by The Department of Clinical Trial Unit, Oslo University Hospital, using computer-generated block randomisation with variable block size and sealed, opaque envelopes. These envelopes were part of the study kit (appendix p 5). Ambulance personnel obtained oral consent before opening the randomisation envelope. Although this is an open-label study and the ambulance personnel were not masked to treatment allocation, the statistician was masked to the allocations in the dataset until the statistical analysis plan was signed and the database was locked.

Procedures

Patients aged 18–69 years received 3 mL inhalational methoxyflurane (Medical Developments NED, Amsterdam, Netherlands), 100 µg intranasal fentanyl (Takeda Pharma, Vallenback Strans, Denmark), or 0·1 mg/kg intravenous morphine (Abcur, Helsingborg, Sweden). Patients aged 70 years or older received 3 mL inhalational methoxyflurane, 50 µg intranasal fentanyl, or 0·05 mg/kg intravenous morphine. In both groups doses were repeated if needed, with an interval of 5 min for fentanyl and morphine, and the maximum doses were 6 mL methoxyflurane, 500 ug fentanyl, and 0·5 mg/kg morphine. The rationale for doses is described in the protocol (appendix pp 16–95). Dose titration to effect was allowed and guided by patients' NRS scores. If pain relief was inadequate despite repeated doses of the study drug, the ambulance personnel were allowed to administer other analgesics, defined as rescue medication. The choice of rescue medication was made at the ambulance personnel's discretion according to local protocols, based on the patient symptoms and underlying conditions (appendix p 6). Although paracetamol normally is considered a basic component of multimodal analgesia, it was not given with the study drugs but was available as one of many options of rescue medication.

Pain NRS, blood pressure, oxygen saturation, pulse rate, and respiratory rate were measured before administration of study drug and after 5 (only NRS), 10, 20, and 30 min, or when handed over to the emergency department (10–160 min after administration; appendix p 7). Ambulance personnel verbally asked patients to report pain NRS scores. Vital measurements were assessed with Life Pack 15 monitor (Stryker, USA). Respiratory rate was automatically measured with an end-tidal carbon monoxide nasal cannula connected to the monitor. The number of intravenous cannulation attempts was noted. Adverse events were monitored by ambulance personnel throughout the prehospital phase. Adverse events were documented in the patient record and reported according to protocol. Additional timepoints were recorded at scene arrival, study drug administration, rescue medication administration, and handover at emergency department or equivalent. Pain diagnoses were grouped into four: chest pain of cardiac origin, traumatic pain, non-traumatic musculoskeletal pain, and other non-traumatic pain. These pain diagnoses were recorded based on hospital records collected within 14 days of the event.

We also recorded patient and ambulance personnel satisfaction with a 5-point Likert Scale. Sex was determined from the patient's national ID number (11 digits) in patient records. The predominant ethnic group within the catchment area was Norwegian, and data on race and ethnicity were not collected. Data were collected using paper forms and the electronic ambulance patient journal system (EWA version 16) and were entered into a study-specific electronic case report form (Viedoc version 4.78). Data integrity was ensured through predefined validation checks, batch reviews, and manual quality control procedures.

Ambulance personnel had a range of levels of education from emergency medical technicians to paramedics and nurses. Ambulance personnel were required to hold permanent employment, have the necessary medical authorisations, and complete 8 h of mandatory training before being permitted to include patients.

Outcomes

The primary endpoint was mean change in pain on a 0–10-point NRS from baseline to 10 min after administration of the study drug. Secondary endpoints were mean change in pain NRS score at 5, 20, and 30 mins after administration; mean changes in vital parameters; time from arrival to treatment and time from arrival to 2-point reduction in NRS; need for rescue medication; time from investigational medicine administration to rescue medication administration; patient and personnel satisfaction; adverse events; and change in Glasgow Coma Scale (GCS) score.

Adverse events were coded using Medical Dictionary for Regulatory Activities (version 25.E) and categorised using the National Institutes of Health Division of AIDS table for grading the severity of adult and paediatric adverse events (appendix pp 16–95). Respiratory

depression was defined as a respiratory rate less than 10 breaths per min. It was not feasible to register the use of the diluter hole in the methoxyflurane device consistently, and hence, the use of the diluter hole was not included in the evaluation of the need for rescue medication.

Statistical analysis

We estimated the sample size using a *t* test, with effect sizes based on previous studies.[3,23,24] The expected reduction in pain NRS score after 10 min was 3·77 for methoxyflurane, 2·54 for fentanyl, and 2·70 for morphine treatment regimens. A common standard variation of 2·12 was used, with the non-inferiority margin of 1·3.[25] To ensure with 90% power that the upper limit of the two-sided 95% CI would exclude a difference less than the margin of 1·3, we needed 88 participants in each group. When including around 10% dropouts, the study required 300 patients for random assignment. The per-protocol analysis set included all patients who received the assigned treatment with no major protocol deviation. Any rescue medication administered before the primary endpoint assessment at 10 min excluded patients from the per-protocol analysis set. Protocol deviations are listed in the appendix (p 8). The full analysis set included all patients who fulfilled the study criteria and were administered the allocated study drug. The safety analysis set included all patients who received any study drug. The primary endpoint was analysed per protocol, and the sensitivity analysis was performed in the full analysis set with imputations.

Null hypotheses (H_0) were: (1) low-dose methoxyflurane is inferior to intranasal fentanyl at reducing pain; (2) low-dose methoxyflurane is inferior to intravenous morphine at reducing pain; and (3) intranasal fentanyl is inferior to intravenous morphine at reducing pain. These were measured by a change in NRS score from 0 min to 10 min after administration:

H_1: h_0: $\mu_{methoxyflurane}-\mu_{fentanyl} \geq \delta_1$, h_a: $\mu_{methoxyflurane}-\mu_{fentanyl} < \delta_1$

H_2: h_0: $\mu_{methoxyflurane}-\mu_{morphine} \geq \delta_1$, h_a: $\mu_{methoxyflurane}-\mu_{morphine} < \delta_1$

H_3: h_0: $\mu_{fentanyl}-\mu_{morphine} \geq \delta_1$, h_a: $\mu_{fentanyl}-\mu_{morphine} < \delta_1$

μ_x is the mean change in pain NRS (NRS at 10 min − NRS at 0 min) with study drug (methoxyflurane, fentanyl, or morphine}, and δ_1 is the non-inferiority margin of 1·3 (appendix pp 96–115).

The primary hypotheses were tested in a hierarchical manner according to the protocol.[21] For each link in the sequence, two study drugs were compared using the linear regressions model $DNRS_{T10} = NRS_{T0}$ + randomisation, where NRS_{T0} is the baseline NRS score and $DNRS_{T10}$ is the change from baseline to 10 min after administration. Hypotheses were tested sequentially using the Wald test,[26] and inferences about the next hypothesis could only be made if the previous hypothesis' null hypothesis was rejected. A null hypothesis was rejected, and non-inferiority established, if the two-sided 95% CI of the corresponding estimated treatment difference in change in NRS at 10 min was below the prespecified inferiority margin of 1·3. The primary outcomes were also summarised with the number and percentage of patients, mean reduction in score, and SD for each treatment group.

For continuous secondary outcomes, pain NRS was analysed similarly to the primary outcome at the other timepoints 5, 20, and 30 min, and vital parameters were analysed at 10 min using ANOVA followed by Tukey's test. For dichotomous secondary outcomes, rescue medication was analysed with a logistic regression model, adjusted for baseline pain scores. For adverse events, no adjustments for baseline scores were made, and Pearson's Chi square test was used. Ordinal outcomes were analysed with a proportional odds model and when model assumptions were not met Kruskal Wallis test or Fisher's exact test were used. Time-to-event was analysed with Cox regression under the assumption that the group hazards were proportional over time. When this assumption was not met, the analysis was performed with a log-rank test. A Kaplan–Meier plot was made for visualisation. For analysing time from ambulance arrival to a 2-point reduction in pain NRS score, linear interpolation was used to estimate the exact time this reduction was achieved if it occurred between two timepoints. Predictors for adverse events were examined as exploratory endpoints.

There were, per definition, no missing data for the primary endpoint in the per protocol analysis set. However, for the sensitivity analysis in the full analysis set, and for secondary outcomes, missing values were imputed using multiple imputation (appendix pp 8–9). All statistical analyses were performed using R version 4.3.3. The Data Monitoring Committee performed a half-way-inclusion assessment (Sept 1, 2022), and the study was monitored throughout the trial period. No interim efficacy analyses were planned.

Role of the funding source

The funders of this study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Nov 12, 2021, and April 22, 2023, 632 patients were assessed for eligibility and 338 were randomly assigned to methoxyflurane (n=112), fentanyl (n=115), or morphine (n=111; figure 1). 281 patients were included in the per-protocol set, of whom 102 were in the methoxyflurane group, 89 in the fentanyl group, 90 in the morphine group. Differences in group sizes were caused by more dosing errors in the morphine and fentanyl groups than in the methoxyflurane group

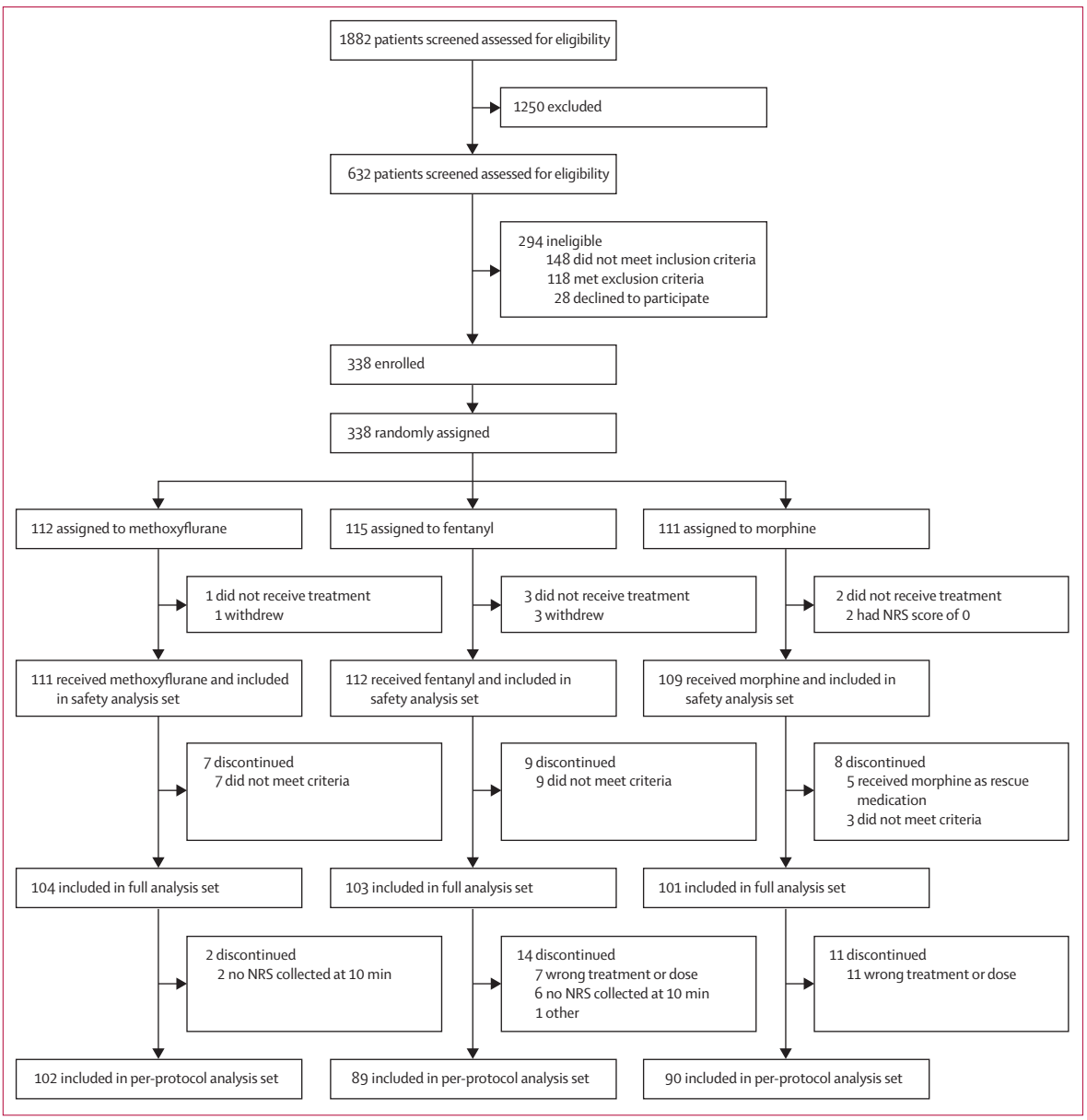

Figure 1: **Trial profile**
NRS=Numeric Rating Scale.

(appendix p 8). Overall, 145 (52%) of 281 patients were female and 136 (48%) were male. Median age was 61 years (IQR 47–75; table).

Mean pain NRS score before treatment was 7·6 (SD 1·8) and mean cumulative doses given up to 10 min were 3·0 mL (0·3) methoxyflurane, 153 µg (53·19) fentanyl, and 8·7 mg (4·03) morphine. The total mean cumulative doses at the end of the study were 3·5 mL (1·2) methoxyflurane, 293 µg (132) fentanyl, and 13·8 mg (7·0) morphine. At 10 min after administration, the mean change in NRS score was –3·31 (2·67) for methoxyflurane, –1·98 (2·28) for fentanyl, and –2·74 (2·12) for morphine (figure 2; appendix p 8). In the linear model, at 10 min, methoxyflurane changed the mean NRS score by –1·33 (95% CI –2·01 to –0·64) compared with intranasal fentanyl (figure 3). The upper limit of the 95% CI was below the non-inferiority margin of 1·3, and methoxyflurane was non-inferior (and showed even superiority) to fentanyl in reducing pain at 10 min. Methoxyflurane changed the mean NRS score by –0·36 (95% CI –1·03 to 0·31) compared with morphine and was non-inferior to morphine. Fentanyl changed the mean NRS score by 0·91 (0·27 to 1·55) compared with morphine, with the 95% CI crossing the non-inferiority margin, and hence, we could not conclude on non-inferiority at 10 min. The 95% CI was in favour of

	Morphine group (n=90)	Fentanyl group (n=89)	Methoxyflurane group (n=102)
Sex			
Male	38 (42%)	47 (53%)	51 (50%)
Female	52 (58%)	42 (47%)	51 (50%)
Age, years	64 (48–76)	61 (50–75)	60 (47–74)
Weight, kg			
Median	76 (68–92)	80 (73–93)	81 (70–90)
Missing	1 (1%)	4 (4%)	9 (9%)
Diagnosis category*			
Chest pain of cardiac origin	3 (3%)	5 (6%)	6 (6%)
Trauma or injury pain	35 (39%)	30 (34%)	29 (28%)
Non-traumatic musculoskeletal	18 (20%)	28 (31%)	28 (27%)
Other non-traumatic pain	34 (38%)	26 (29%)	39 (38%)
Systolic blood pressure, mm Hg	150 (23·2)	153 (25·5)	151 (24·3)
Diastolic blood pressure, mm Hg	86 (17·8)	86 (14·3)	84 (15·2)
Pulse rate, min^{-1}	80 (70–94)	80 (70–93)	80 (69–89)
Respiratory rate, min^{-1}	18 (16–20)	18 (16–20)	18 (16–20)
Oxygen saturation			
Median	97% (95–99)	98% (96–99)	97% (96-99)
Missing	0	0	1 (1%)
Glasgow Coma Scale	15 (15–15)	15 (15–15)	15 (15–15)
Numeric Rating Scale	7 (5–9)	8 (7–9)	8 (6–9)

Data are n (%), median (IQR), or mean (SD). Baseline data were collected during screening. There were no missing data for variables unless included in the table. *Full diagnosis overview is provided in the appendix (p 15).

Table: **Demographic and baseline characteristics of the per-protocol population**

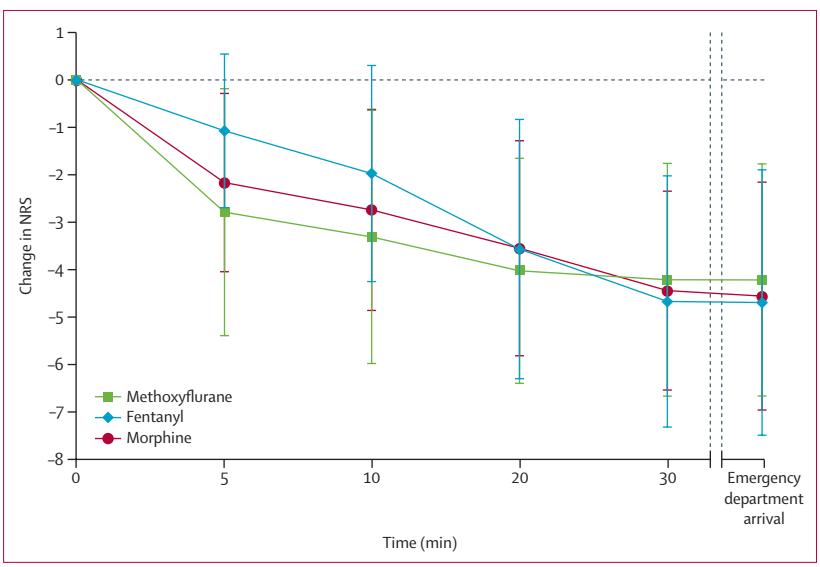

Figure 2: **Pain relief efficacy measured by change in NRS score over time**
The figure shows the change in mean pain NRS score for morphine (red), fentanyl (blue), and methoxyflurane (green). Timepoints are time since administration of study medication. Lines represent mean change, and bars represent change by 1 SD. NRS=Numeric Rating Scale.

morphine. At 5 min after administration, methoxyflurane showed an even larger margin. On average, methoxyflurane changed mean pain NRS scores by –1·70 (–2·30 to –1·10) compared with intranasal fentanyl and –0·47 (–1·10 to 0·18) compared with morphine, whereas intranasal fentanyl was inferior to morphine with a pain reduction difference of 1·14 (0·62 to 1·66) in favour of morphine. The differences levelled at 20 min and 30 min, however, confirming non-inferiority for all three comparisons (figure 3). The sensitivity analysis on all timepoints performed in the full analysis set supported the results from the per-protocol analysis set analyses (appendix p 9). Subgroup analyses for the primary endpoint at 10 min were performed on sex, age, and diagnostic categories. In general, the main findings were consistent across all subgroups, although for methoxyflurane, non-inferiority was not determined for some of the diagnostic categories with fewest patients (figure 4).

None of the patients in the per-protocol analysis set received any rescue medication during the first 10 min, and the primary endpoint was, hence, a result of the allocated study drug. Subsequently, rescue medication was given to 14 (16%) of 90 patients in the morphine group, 26 (29%) of 89 in the fentanyl group, and 41 (40%) of 102 in the methoxyflurane group (appendix p 10). In a logistic regression model with adjustment for baseline pain NRS score, methoxyflurane was a significant predictor for needing rescue medication, with an odds ratio (OR) of 3·4 (p=0·0008), whereas intranasal fentanyl had an OR of 2·0 (p=0·060). The median time from administration of study drug to rescue medication

was significantly shorter for methoxyflurane than for the other groups (hazard ratio 2·5 [95% CI 1·37 to 4·66]; p=0·0030; appendix p 11). The mean cumulative doses of study drug received by the time of first administration of rescue medication were 13·4 mg (SD 6·8) morphine, 287 µg (128·8) fentanyl, and 3·5 mL (1·1) methoxyflurane.

Vascular access was established, or attempted to be established, in 211 (75%) of 281 patients, of whom 59 (28%) needed more than one cannulation attempt. In 68 (24%) of 281 patients, vascular access was not attempted: two (2%) of 90 in the morphine group (for whom intravenous access was already established), 28 (31%) of 89 in the fentanyl group, and 38 (37%) of 102 in the methoxyflurane group. 66 (35%) of 191 patients in the two non-intravenous groups did not receive any vascular access attempt, and invasive procedure was avoided (appendix p 12).

There was a significant difference in the time from the ambulance arriving at the scene to administering study drug, with a median time of 22·5 min (95% CI 21–26) for intravenous morphine, 17 min (15–19) for fentanyl, and 18 min (17–20) for methoxyflurane (p=0·0020; appendix p 11). The median time from administration of the first dose of study drug to a 2-point reduction in pain NRS score was 30·0 min (95% CI 27·5–34·0) in the morphine group, 29·0 min (26·3–35·0) in the intranasal fentanyl group, and 25·3 min (22·3–32·5) in the methoxyflurane group (p=0·70; appendix p 11). Patient satisfaction was good or better for 67 (77%) of 87 patients in the morphine group, 63 (71%) of 89 in the fentanyl group, and 68 (69%) of 99 in the methoxyflurane group. Excellent satisfaction was highest in the methoxyflurane group (42 [42%] of 99), but poor satisfaction was also the highest in this group (21 [21%] of 99). These findings are also reflected in the corresponding study worker satisfaction scoring (appendix p 12).

Of all patients, only one had a 2-point reduction in GCS score and nine had a 1-point reduction at 10 min. Only 1-point reductions in GCS were observed thereafter. Eight (80%) of ten reductions in GCS score at 10 min were in the methoxyflurane group, but the overall difference between the three groups was not significant (p=0·051). There were no significant differences in reduction of systolic blood pressure or change in respiratory rates between the groups (appendix p 13). In total, 94 adverse events were recorded in 77 (23%) of 332 patients: 24 (22%) of 111 in the methoxyflurane group, 27 (24%) of 112 in the fentanyl group, and 26 (24%) of 109 in the morphine group (appendix pp 13–14). There were no differences between the groups and frequency of adverse events (p=0·89). The overall most common adverse events were vomiting (36 [11%] of 332), nausea (15 [5%]), respiratory depression (12 [4%]), and dizziness (six [18%]). Only two events were defined as severe adverse events with respiratory depression and loss of consciousness. Both occurred in the same patient in the methoxyflurane treatment group, but after administration of rescue medication. There were no treatment-related deaths. A purposeful selection method in a logistic regression model was used to identify predictors of adverse events, testing baseline NRS scores, treatment group, sex, provider education level, age, and rescue medication before the adverse event. The most parsimonious model retaining predictive value included only sex: women had a higher risk for adverse events than men (OR 2·07; p=0·013).

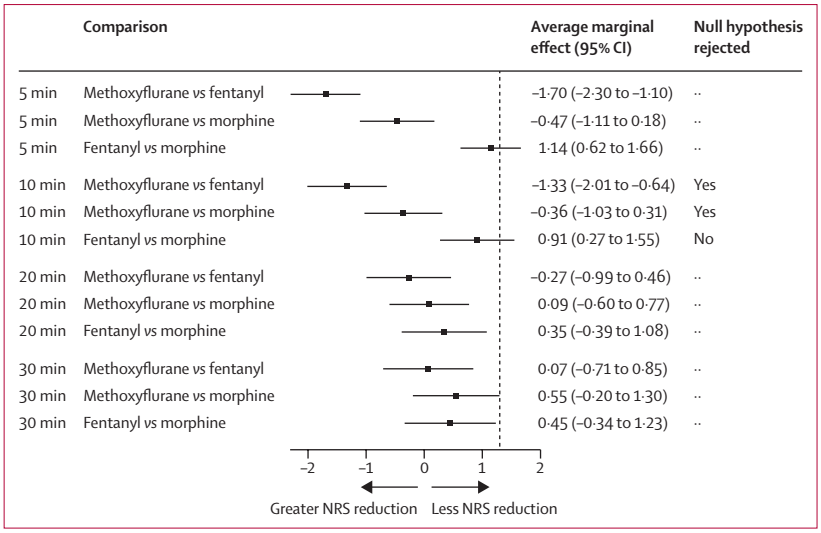

Figure 3: **Estimated difference in NRS score between treatment groups in the per-protocol analysis set**
The average marginal effect is measured across all observations using a balanced grid of covariates (if applicable). Change in NRS score at 10 min is the primary outcome. The other timepoints are secondary outcomes. For each timepoint, hypotheses 1–3 were tested sequentially and therefore no further adjustment for multiple testing were done. The dashed line represents the non-inferiority margin. NRS=Numeric Rating Scale.

Discussion

This randomised, non-inferiority trial shows that methoxyflurane is non-inferior to intravenous morphine and intranasal fentanyl for treating acute moderate to severe pain, measured 10 min after administration. Although methoxyflurane showed equal superiority to intranasal fentanyl, the study design only allowed for conclusion of non-inferiority. Notably, methoxyflurane showed effectiveness shortly after administration compared with opioids. The differences in effectiveness between groups levelled after 20 and 30 min, but the non-inferiority of methoxyflurane to intravenous morphine and intranasal fentanyl remained. Intranasal fentanyl was not shown to be non-inferior to intravenous morphine at 10 min.

A systematic review[20] suggests that methoxyflurane is a short-acting, single analgesic that bridges intravenous access with administration of other analgesics. This recommendation is based on a few low-quality studies. Our trial provides high-quality evidence supporting these previous findings. In a randomised crossover study, inhaled methoxyflurane was equianalgesic to 25 µg intravenous fentanyl during a cold pressor test.[17] Our

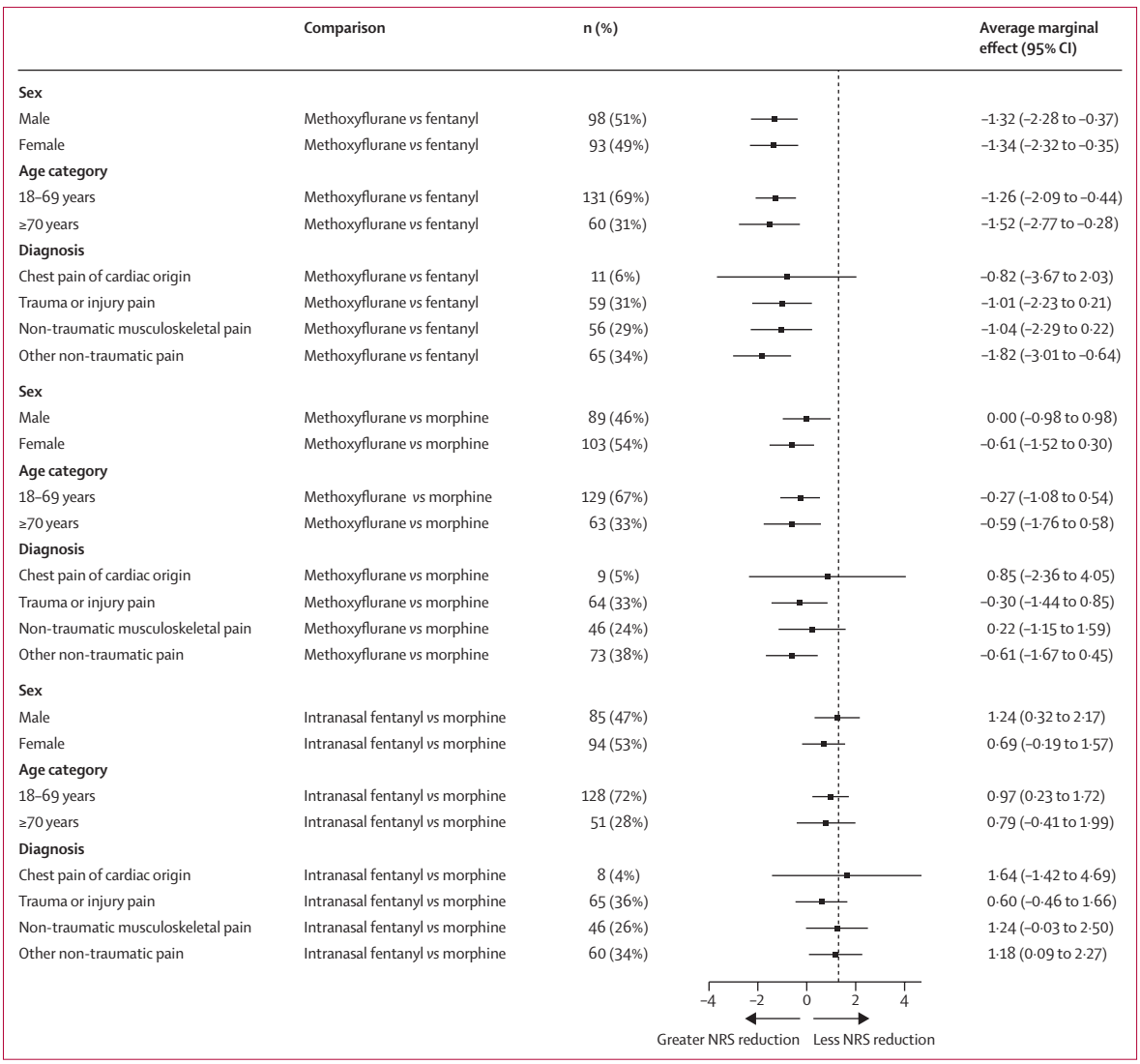

Figure 4: **Subgroup analysis 10 min after first dose of study drug**
The average marginal effect is measured across all observations using a balanced grid of covariates (if applicable). Differences in change in NRS score 10 minutes after first study drug dose between treatment groups, stratified by subgroups, using the per-protocol analysis set. The dashed line represents the non-inferiority margin. NRS=Numeric Rating Scale.

clinical study showed a notable timely difference in effectiveness compared with fentanyl and morphine and non-inferiority to a higher dose than 25 µg intravenous fentanyl. This finding suggests that the rapid onset of effect and the self-administration of methoxyflurane might enhance its perceived analgesic properties in a clinical prehospital setting. The titration of analgesics is crucial for an effective pain relief strategy, which contrasts with experimental studies with single doses.[27] Our individualised management of intravenous morphine and intranasal fentanyl regimens resulted in higher accumulated doses than those in previous literature.[18,27,28] However, given the dosage restrictions imposed by the device, which are limited to 50 or 100 µg per dose for intranasal fentanyl, the initial dosage might appear inadequate compared with the total accumulated dose.

The need for rescue medication is a surrogate marker of the effectiveness of the allocated analgesic treatment. In our study, 76 (84%) of 90 patients in the morphine group, 63 (71%) of 89 in the fentanyl group, and 61 (60%) of 102 in the methoxyflurane group did not need any rescue medication throughout the prehospital phase. The difference in the need for rescue medication between the fentanyl and morphine groups was not significant. This finding is in line with a literature review[4] that found that intravenous morphine and intranasal fentanyl had similar effects. Although most of the patients with non-intravenous analgesics were managed adequately without rescue medication, the differences in

need for rescue medication suggests that methoxyflurane might not provide adequate pain control during the whole prehospital phase. We cannot rule out that the large number of patients who received rescue medication in the methoxyflurane group affected the non-inferiority result at 20 and 30 min. However, with its rapid onset of effect, methoxyflurane could serve as a good option for the early stages of treatment.

Overall, all three study drug regimens had mild, transient adverse events that were consistent with expected pharmacological action. The frequency of these adverse events was similar across treatment groups and are consistent with earlier studies.[11,20] It is noteworthy that motion sickness during transport and pain itself can cause nausea and vomiting, as described in the most frequent adverse events. The only significant predictor for adverse events in our study was female sex, which is in line with a retrospective study.[29]

No subgroup analyses differed distinctly from the main findings, but there were wider 95% CIs in the smaller subgroups, such as in the category of diagnosis of chest pain (figure 4). It is noteworthy that the effectiveness in the young and old subgroups was identical for all three comparisons. Although methoxyflurane is approved in Europe for moderate to severe pain in adult patients with trauma-associated pain, our results indicate a rapid onset of action across all diagnostic groups. Studies suggest there should be more focus on non-opioid analgesia to treat chest pain due to the concern of increased myocardial infarction severity by higher opioid doses.[30] In our study, the subgroups with chest pain of cardiac origin were too small to conclude whether there was any difference in effect between the study drugs.

In addition to evaluating pain levels using the NRS, we assessed satisfaction levels (using a Likert Scale) among personnel and patients, recognising that these measures are distinct. Our findings show a notable dichotomy in the methoxyflurane group, with a predominance of excellent and poor scores among personnel and patients. This finding suggests a dual phenomenon associated with methoxyflurane: although its overall analgesic effectiveness over time is lower than that of opioids (ie, necessitating additional rescue medication for some individuals), its rapid onset of pain relief and provision for self-administration might empower patients by enhancing their perceived control.

This study used oral consent from the patients, which represents a departure from the conventional requirement for written consent. The ethical considerations surrounding the recruitment of patients with moderate to severe pain for a clinical study are complex. They involve balancing the need to minimise delays in acute care against the imperative to ensure that patients fully understand what they are consenting to. Consequently, we implemented several mitigating measures, including exclusion criteria guided by contextual judgement, specialised training for study personnel on obtaining credible consent, providing written information to all patients about how to withdraw from the study, and establishing a protocol for the study team to attempt follow-up calls with all patients 2 weeks post-inclusion. Obtaining consent in the acute prehospital setting is challenging; however, we believe that our implemented measures effectively balance these ethical considerations, ensuring appropriate medical treatment and informed consent. Ultimately, seven patients withdrew from the study: five during treatment, one during the 2-week follow-up call, and one post-treatment through the contact details provided in the written information.

The open-label design might introduce expectation bias but was chosen due to practical and ethical considerations. A double-blinded, triple-dummy study would be too complicated and time-consuming in the acute prehospital setting. Our real-life approach is, however, pragmatic and corresponds to standard medical practice. Additionally, the primary outcome of change in NRS score after 10 min, represents a highly relevant, subjective patient-reported outcome. The 10-min timepoint was selected due to its clinical and operational relevance in the acute prehospital setting, where prompt analgesic effect is essential. However, this early assessment is limited by the pharmacodynamic and pharmacokinetic properties of the three study drugs, particularly before full effect is achieved for some of them. Notably, inhalation administration typically has a shorter time-to-effect, whereas intranasal administration has a longer onset. The experience of pain includes objective and subjective elements, influenced by the situation, pain response, and patient experience. All personnel received specific training and simulation exercises in how to score NRS. Although this was a single-centre study, it was conducted across three different locations, covering both urban and rural areas. The modest eligibility rate (632 [34%] of 1882 patients) could be affected by the study setting, where the threshold for including patients is dependent on high motivation among the study workers. In addition, many patients with acute pain were not eligible for inclusion due to dementia, confusion, language problems, or complex symptoms, and the ambulance workers might have avoided active exclusion for various reasons. We have no reason to believe that the study population diverges from the patient population of interest. The manual entry of data into the database presents a potential risk to data integrity. Nonetheless, predefined validation checks and rigorous quality control procedures were implemented to ensure reliability of the data.

In conclusion, the PreMeFen study showed that methoxyflurane was non-inferior to intravenous morphine and intranasal fentanyl for treating acute moderate to severe traumatic and non-traumatic pain in the prehospital setting 10 min after administration. Intranasal fentanyl was, however, not shown as

non-inferior to intravenous morphine at 10 min. Although the non-inferiority of methoxyflurane remained throughout the observation time, patients in the methoxyflurane group needed more rescue medication than those in the morphine group.

Contributors

FH and LOF contributed to the conceptualisation of the study. FH and ICO were responsible for the study design. FH and LOF developed the methodology. RS managed the day-to-day operations of the study. RS and LS collated data. KT conducted the statistical analyses. ICO independently checked the primary analysis. RS, LS, and KT performed data validation. RS wrote the original draft. FH and LOF contributed to writing of the original draft. All authors participated in the review and editing of the paper. FH and RS had final responsibility for the decision to submit for publication. RS, FH, LS, and KT accessed and verified the data. All authors had full access to all the included data and approved the final submitted version of the report.

Declaration of interests

We declare no competing interests.

Data sharing

Anonymised individual data and data dictionary will be available for research purposes by request to the corresponding author. Clinical study results will be posted in the European Clinical Trials Database.

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