Trials

STUDY PROTOCOL

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Fentanyl or esketamine for traumatic pain (FORE-PAIN) trial: study protocol for a double-blind multi-arm randomized non-inferiority trial

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Abstract

Background Although fentanyl and esketamine, administered intravenously (IV) or intranasally (IN), are standard of care for treatment of acute traumatic pain in the prehospital setting in the Netherlands, comparative evidence regarding their efficacy and safety is lacking. Therefore, this study aims to assess the efficacy and safety of fentanyl IN, esketamine IV and esketamine IN as compared to fentanyl IV for management of acute traumatic pain in the prehospital setting.

Methods This is a double-blind, monocenter, multi-arm, randomized non-inferiority trial in the prehospital setting in the Netherlands. Adult subjects receiving emergency care from Emergency Medical Services Ambulance Amsterdam and suffering from acute severe traumatic pain are randomized in an 1:1:1:1 ratio to receive fentanyl IV (1.0 µg/kg), fentanyl IN (1.25 µg/kg), esketamine IV (0.2 mg/kg), or esketamine IN (0.625 mg/kg). The primary endpoint is the reduction in Numeric Rating Scale (NRS, 0–10) score at 10 min after first administration of study medication. The prespecified non-inferiority margin is 1.0 for the between-group absolute difference in primary outcome. The primary endpoint is analyzed according to the intention-to-treat and per-protocol principles conforming to recommendations for non-inferiority analysis. Other endpoints include reduction in NRS score at other timepoints, need for additional analgesia, patient satisfaction, and adverse events.

Discussion This trial is one of few double-blind randomized controlled trials in the prehospital setting and aims to answer questions that have relevance to prehospital practice. Research in a prehospital emergency setting also comes with challenges, including concerns about prehospital data quality, limited research experience among personnel and a limited timeframe for data collection and follow-up. Also, informed consent needs to be deferred.

Trial registration ClinicalTrials.gov NCT06051227. Registered on 9 September 2023.

Keywords Fentanyl, Esketamine, Emergency medical services, Acute pain, Wounds and injuries, Analgesia, Administration, Intravenous, Intranasal

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Administrative information

Note: The numbers in curly brackets in this protocol refer to SPIRIT checklist item numbers. The order of the items has been modified to group similar items (see http://www.equator-network.org/reporting-guidelines/spirit-2013-statement-defining-standard-protocol-items-for-clinical-trials/).

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Name and contact information for the trial sponsor {5b}	Amsterdam UMC Meibergdreef 9, 1105 AZ Amsterdam
Role of sponsor {5c}	The sponsor is responsible for, and has ultimate authority over, study design, management, analysis and interpretation of data, writing of the report and the decision to submit the report for publication. The funder has no role in any of the mentioned fields.

Introduction

Background and rationale {6a}

Acute traumatic pain requires immediate analgesia. Inadequate pain treatment increases patient suffering, hampers access to the patient as well as necessary treatment and transportation, and increases the stress response [1]. However, prehospital pain management remains a challenge and the majority of trauma patients report sustained pain upon arrival at the emergency department (ED) [2, 3]. Traditionally, severe traumatic pain is treated with intravenous (IV) opioids. Fentanyl is often the analgesic of choice and is standard of care in many acute and prehospital pain management guidelines [4–10]. Alternatively, severe traumatic pain can be treated with IV ketamine [5–8]. In some European countries, such as The Netherlands, esketamine is used, an enantiomer of racemic ketamine which provides twice the analgesic potency [11, 12]. However, no studies have directly compared fentanyl and esketamine for treatment of traumatic pain in adults.

While IV administration of analgesics leads to the highest bioavailability and shortest time of onset, obtaining IV access takes time and is not always easy to perform in the prehospital setting [13]. Intranasal (IN) administration is an easy to use and minimally invasive alternative with a short time of onset [14]. IN administration of fentanyl and ketamine or esketamine is well known and included in several acute and prehospital pain management guidelines [5–10, 15]. However, no study has compared the efficacy of IV administration of fentanyl or esketamine to IN administration.

Dutch prehospital pain management guidelines include all four mentioned options: fentanyl IV, fentanyl IN, esketamine IV, and esketamine IN [9, 10]. However, comparative evidence regarding the efficacy and safety of these options in trauma patients is lacking. Therefore, this study aims to evaluate the efficacy and safety of esketamine IV, fentanyl IN, and esketamine IN compared with fentanyl IV for treatment of acute traumatic pain in adults in a randomized, controlled, double-blind non-inferiority trial.

Objectives {7}

Primary objective

To determine whether fentanyl IN, esketamine IV, and esketamine IN are non-inferior to fentanyl IV for treatment of acute traumatic pain in the prehospital setting.

Secondary objectives

- To determine the effect of fentanyl IN, esketamine IV, and esketamine IN on patient satisfaction with regard to analgesia as compared to fentanyl IV
- To determine the safety of fentanyl IN, esketamine IV, and esketamine IN as compared to fentanyl IV

Trial design {8}

The FORE-PAIN trial is a double-blind, double-dummy, multi-arm, parallel-group, randomized, non-inferiority

trial that investigates the use of four different methods of analgesia (allocation 1:1:1:1 ratio). Emergency Medical Services (EMS) personnel were extensively involved in the design of the trial. There was no patient involvement in the protocol as we experienced difficulty identifying appropriate representation of the study population (prehospital trauma patients),

Methods: participants, interventions and outcomes

Study setting {9}

Study setting is the prehospital setting in the region of EMS Ambulance Amsterdam, which centers around Amsterdam, the Netherlands.

Eligibility criteria {10}

In order to be eligible to participate in this study, a subject must meet all of the following criteria:

- Age ≥ 18 years,
- Presence of pain that was caused by an acute trauma (any trauma mechanism) that occurred on the same day,
- EMS personnel determine that administration of fentanyl or esketamine for analgesia is required, and
- Subject will be transported to a hospital.

A potential subject who meets any of the following criteria will be excluded from participation in this study:

- Reported or estimated weight <40 or >100 kg,
- Subject does not understand Dutch or English,
- Subject is known to have previously declined participation in medical research,
- Subject is unable to report pain scores,
- Inability to give IN or IV medication,
- Known severe cardiovascular disease,
- Pre-eclampsia, and
- Glasgow Coma Scale score < 11.

Who will take informed consent? {26a}

Considering the emergency setting of this trial, deferred consent is applied in accordance with article 35 of the EU Clinical Trials Regulation. The earliest opportunity at which informed consent can be obtained, is after the subject has arrived at the hospital and is able to oversee his/her situation adequately. At this point, all study procedures have been completed and all data have been collected. This means that informed consent is obtained after the subject has already completed his/her participation in the trial. Informed consent is obtained by an investigator from the clinical trial site.

Additional consent provisions for collection and use of participant data and biological specimens {26b}

Consent for collection and use of participant data in possible follow-up studies is included in the informed consent procedure. Biological specimens are not collected.

Interventions

Explanation for the choice of comparators {6b}

Fentanyl IV can be considered the gold standard, since opioids are the oldest and most well-known analgesic drugs [16]. Therefore, Fentanyl IV is chosen as active comparator.

Intervention description {11a}

All subjects receive IV access, followed by one dose of study medication (i.e., fentanyl IV, fentanyl IN, esketamine IV or esketamine IN). To ensure blinding, a placebo (NaCl 0.9%) is administered through the alternative route of administration (e.g., when receiving fentanyl IV, a subject receives placebo IN). A second dose of study medication can be administered after 10 min if required. If a subject requires more than two doses of study medication, he/she is unblinded (considered treatment failure). The subject then continues to receive regular medical care. At any time after determination of the primary endpoint (10 min), the EMS personnel are free to administer paracetamol or diclofenac in line with Dutch EMS guidelines.

Fentanyl IV

The initial dose of 1.0 μg/kg is in line with Dutch EMS guidelines, which describes a range of 1–4 μg/kg [9]. If required, an additional dose of 0.6 μg/kg (60% of initial dose) can be administered after 10 min, resulting in a maximum total dose of 1.6 μg/kg.

Fentanyl IN

The initial dose of fentanyl IN (1.25 μg/kg) is in accordance with Dutch EMS guidelines, which describes a range of 1–4 μg/kg [9]. The increased dose of fentanyl IN compared to fentanyl IV is based on studies on bioavailability and efficacy. The bioavailability for fentanyl solution used for IN administration has been reported to be as low as 71% [17]. Significant analgesic efficacy has been shown within a dose range of 1–2 μg/kg [18].

Considering the concentration of the fentanyl solution (50 μg/ml) and the maximum volume that can be administered IN (2 ml, 1 ml per nasal cavity), the maximum initial dose is 100 μg. This dose is reached at a dosing weight of 80 kg, resulting in a relative dose decrease for patients with a higher weight.

However, this relative dose decrease for these patients is corrected if the patient requires a repeated dose: if required, an additional dose of 1.0 µg/kg can be administered after 10 min, up to a maximum total dose of 2.0 µg/kg. This means that patients with a dosing weight ≤80 kg will receive an additional dose of 0.75 µg/kg (60% of initial dose), while patients >80 kg will receive a relatively larger second dose.

Esketamine IV

The initial dose of esketamine IV (0.20 mg/kg) is in accordance with Dutch EMS guidelines, which describes a range of 0.10–0.25 mg/kg [9]. If required, an additional dose of 0.12 mg/kg (60% of initial dose) can be administered after 10 min, resulting in a maximum total dose of 0.32 mg/kg.

Esketamine IN

Initial dose of esketamine IN (0.625 mg/kg) is in accordance with Dutch military prehospital guidelines, which describes a dose of 50 mg for an average person of 80 kg [10]. The increased dose of esketamine IN compared to esketamine IV is based on studies on bioavailability and efficacy. The bioavailability for esketamine solution used for IN administration has been reported to be as low as 30–50% [19]. Significant analgesic efficacy has been shown within a dose range of 0.45–1.25 mg/kg [20]. Racemic ketamine is more common in international pain management and also has proven efficacy when administered IN, generally using a dose of 1 mg/kg [21].

Considering the concentration of the used solution (25 mg/ml), the maximum initial dose for IN administration is 50 mg. This dose is reached at a dosing weight of 80 kg, resulting in a relative dose decrease for patients with a higher weight. Similarly to fentanyl IN, this relative dose decrease for these patients is corrected if the patient requires a repeated dose: if required, an additional dose of 0.5 mg/kg can be administered after 10 min, up to a maximum total dose of 1 mg/kg. This means that patients with a dosing weight ≤80 kg will receive an additional dose of 0.375 mg/kg (60% of initial dose), while patients >80 kg will receive a relatively larger second dose.

Criteria for discontinuing or modifying allocated interventions {11b}

Criteria for withdrawal from the study are:

- Subject wants to leave the study. This is possible at any time for any reason.

Criteria for withdrawal from study medication are:

- EMS personnel decide to withdraw subject for urgent medical reasons, for example adverse events,
- EMS personnel become aware of or subject develops any of the exclusion criteria.

Strategies to improve adherence to interventions {11c}

EMS personnel are responsible for administration of the study medication. They will complete a study specific training before the recruitment period starts. The administered dose of study medication is recorded in the Case Report Form (CRF).

Relevant concomitant care permitted or prohibited during the trial {11d}

EMS personnel are free to administer paracetamol and/or diclofenac in line with EMS guidelines, after the primary endpoint has been recorded.

At any time, EMS personnel are free to administer 1 mg of midazolam IV for treatment of unpleasant psychomimetic side effects of esketamine. Since EMS personnel are blinded to the study arm, it is theoretically possible that midazolam will be given to a subject who received fentanyl. Although both fentanyl and midazolam can cause sedation, the dosages of both drugs (especially the very low dose of 1 mg midazolam) are such that the combination is not expected to lead to oversedation. Any other adverse events are treated at the discretion of EMS personnel in accordance with EMS guidelines.

Provisions for post-trial care {30}

Provisions for ancillary and post-trial care are not arranged, since participation in this trial is not expected to have long-term effects. The sponsor does have a trial participant and liability insurance.

Outcomes {12}

Primary outcome is the change in Numeric Rating Scale (NRS) pain scores between baseline and 10 (8–12) min after administration of the first dose of study medication. Earlier research has indicated that significant pain reduction can be expected at this timepoint [22–24]. The NRS pain score is an 11-point Likert scale ranging from 0 to 10, where 0 means "no pain" and 10 means "worst pain imaginable." It is a validated, simple and fast tool for measurement of pain intensity and standard of care in Dutch EMS [25]. It is also one of the most used tools internationally and recommended by the European Society for Emergency Medicine [8].

Secondary outcomes providing information on efficacy of the study arms are:

	Enrolment	Post-allocation				Close-out
TIMEPOINT*	$-t_1$	t_0	t_1	t_2	t_3	t_4
ENROLMENT:						
Eligibility screen	X					
Allocation	X					
Informed consent ('deferred')						X
INTERVENTIONS:						
[Fentanyl IV, Fentanyl IN, Esketamine IV, Esketamine IN]		X	X**	X**		
ASSESSMENTS:						
[NRS score]		X	X	X	X	
[Requirement for extra analgesia]			X	X		
[subject satisfaction]					X	
[adverse events]			X	X	X	

Fig. 1 SPIRIT 2013. *–t_1 = arrival at subject, t_0 = baseline, t_1 = 10 (8–12) min), t_2 = 20 (16–24) min, t_3 = arrival at hospital, t_4 = after arrival at hospital. ** If required, study medication can be repeated once

– (Relative) change in NRS pain score between baseline and different timepoints after administration of study medication (20 min, arrival at the hospital).
– Number of subjects requiring a second dose of study medication.
– Number of subjects requiring unblinding because of treatment failure (i.e., requiring more than two doses of study medication).
– Patient satisfaction with prehospital analgesia on an 11-point Likert scale (0 = extremely unsatisfactory, 10 = extremely satisfactory).

Secondary outcomes providing information on safety of the study arms:

– Number of subjects experiencing (serious) adverse events.
– Number of subjects requiring an intervention to treat (serious) adverse events, specifically midazolam.
– Number of subjects requiring unblinding because of (serious) adverse event.

Participant timeline {13}

Subjects are screened and included by EMS personnel as soon as possible after arriving at the patient. All study procedures and data collection are completed upon arrival at the hospital by ambulance. Informed consent is obtained afterwards. A schematic diagram is included below (Fig. 1).

Sample size {14}

Sample size calculation is focused on demonstrating non-inferiority of each intervention arm to the comparator arm for the primary endpoint. The following parameters were used to calculate the overall sample size:

- An overall 1-sided significance level of 0.025, which means 0.025/3=0.0083 for three pairwise comparisons to control for type I error (Bonferroni correction); a 1-sided alpha of 0.025 is considered to be more robust for non-inferiority assessment and preserves consistency between significance testing and subsequent estimation with conventional 2-sided 95% confidence intervals (i.e., 98.34% adjusted for

three pairwise comparisons); this provides additional information in the situation in which any of the alternative treatments appears superior to the reference treatment [26].
- Eighty percent power;
- A within-group SD of 2.6 based on previous data [27–29]; and
- A non-inferiority margin of 1.0 for the between-group difference in primary outcome.

The non-inferiority margin corresponds to 25–33% of an estimated mean 3–4 point decrease (on an 11 point scale) of NRS pain score 10 min after one dose of any of study medication [27–29]. We consider a difference of 1.0 as the maximal acceptable decrease in pain reduction for non-inferiority, taking into account the advantages of the intervention arms (i.e., IN administration in situations where IV access is not (readily) available and the use of esketamine in patients with suspected hypovolemia or respiratory depression). The reported absolute minimum clinically important difference varies significantly in acute pain studies, ranging from 8 to 40 mm (on 0–100 mm scale) [30]. A non-inferiority margin of 1.0 approaches the lowest minimum clinically important difference that has been reported in acute pain and we therefore consider differences below this threshold to be clinically irrelevant. This margin has also been used previously in a similar study [23].

When the sample size in each group is 144, a one-sided 0.0083 significance level two group *t*-test for the difference in means of the primary outcome will have 80% power to reject the null hypothesis that the intervention arm is inferior to the comparator arm by a margin of 1.0 in favor of the alternative hypothesis that the intervention arm is non-inferior to the comparator arm, assuming no difference in primary outcome means and a common standard deviation of 2.6. Given the short duration of the study, we expect a low drop-out of 5%, thereby requiring 152 subjects per study arm, which brings the total number of required subjects to 608.

Recruitment {15}

The subjects will be recruited from all patients suffering from traumatic pain, who are attended to by EMS Ambulance Amsterdam. EMS Ambulance Amsterdam receives about 16,000 calls per year in the category "trauma/surgery," of whom approximately 4000 receive fentanyl and/or esketamine and are transported to the hospital. Difficulties in recruiting the required number of subjects from this population within the available period (18 months) are not expected.

Assignment of interventions: allocation

Sequence generation {16a}

The allocation sequence has been generated by a statistician of the Department of Epidemiology and Data Science of the sponsor. It has been generated using computer-generated random numbers, block randomization with varying block sizes (4–24), no stratification and with a 1:1:1:1 allocation ratio.

Concealment mechanism {16b}

The allocation sequence has been provided to the pharmacy of the sponsor. Pharmacy personnel (who are unblinded) assemble study kits using the allocation sequence. Study kits look identical, ensuring blinding of EMS personnel and the subject.

Implementation {16c}

The allocation sequence has been generated by a statistician of the Department of Clinical Epidemiology and Data Science of the sponsor and provided to the pharmacy of the sponsor, where study kits are assembled accordingly. Subsequently, the study kits are transported to the participating EMS stations where they can be used by EMS personnel. EMS personnel are responsible for enrollment of subjects. Since EMS personnel are blinded to the content of the study kit, assignment of participants to interventions occurs at random.

Assignment of interventions: blinding

Who will be blinded {17a}

This is a double-blind, double-dummy study, where both EMS personnel and the subject are blinded to the treatment allocation. EMS personnel are provided with study kits which look identical for each study arm.

Procedure for unblinding if needed {17b}

Immediate unblinding is allowed in certain predefined situations, e.g., in case of a medical emergency. Each study kit contains a sealed envelope, which states what study medication has been given and through which route. Need for unblinding will be recorded in the case report form. Unblinding is also permissible after the subject completed participation if required for safety reporting by the sponsor. A standard unblinding request form is available.

Data collection and management

Plans for assessment and collection of outcomes {18a}

All data are collected by EMS personnel directly from the subject. EMS personnel will complete a study specific training before the recruitment period, promoting data quality. After informed consent has been obtained,

data are entered into an electronic CRF (eCRF) in Castor EDC, which is regulatory compliant software.

Plans to promote participant retention and complete follow-up {18b}

Given the short duration of our study, loss to follow-up is expected to be low. Subjects who discontinue or deviate from intervention protocols will be included in the intention-to-treat analysis. If a subject wants to leave the study, data collection stops immediately. If a subject is only withdrawn from receiving (additional) study medication, data collection after withdrawal is limited to the primary outcome and adverse events present at withdrawal.

Data management {19}

Data will be collected and processed in accordance with the General Data Protection Regulation (EU) 2016/679, Good Clinical Practice and other relevant regulations. The data will be stored for 25 years in accordance with the Dutch Medical Treatment Contracts Act (Dutch: Wet op de Geneeskundige Behandelingsovereenkomst).

Data are manually entered into an eCRF in Castor EDC, which is Good Clinical Practice (GCP) compliant software. Univariate checks including minimum and maximum values and range checks are in place. The eCRF has been tested by multiple members of the study team. To promote data quality, Source Data Verification is performed by the Clinical Monitoring Center of the sponsor. A detailed data management plan is available and has been approved by a data management expert from the department of Research Data Management of the sponsor.

Confidentiality {27}

Personal information for patients that were ineligible will not be collected. Personal information of enrolled subjects is collected as standard of care data in the electronic patient file. Data are pseudonymized before being entered into an eCRF to protect confidentiality. An identification log is maintained. If the subject does not provide informed consent, anonymous data can be used if the subject does not actively object to the use of data (in line with Article 35 of the Clinical Trials Regulation).

Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in this trial/future use {33}

Not applicable; no biological specimens are collected.

Statistical methods

Statistical methods for primary and secondary outcomes {20a}

The primary analysis compares the primary endpoint between the three intervention arms and the comparator arm for non-inferiority. The use of parametric models on data from Likert scales is standard practice in statistics [31, 32]. Analysis will be performed based on the intention-to-treat and per-protocol principles to evaluate consistency of both analysis approaches compliant with recommendations for non-inferiority analyses [33].

The primary analysis uses a mixed effect model to estimate the treatment group parameter for the primary endpoint of change in NRS pain score at 10 min. We plan to include change in NRS pain score at 20 min (secondary endpoint) in our model to obtain a more precise estimate of change in NRS pain score at 10 min (primary endpoint), assuming positive correlation and common variance. Model assumptions will be assessed by goodness-of-fit testing and by reporting the simpler general linear model as a sensitivity analysis. If the model assumptions are not met, the general linear model will be used (analysis of covariance) as the primary analysis with only the primary endpoint as dependent variable. Baseline NRS pain score is included as covariate in both analyses.

For each intervention arm non-inferiority to the comparator arm can be claimed if the lower limit of the two-sided 98.34% CI for the between-groups (comparator minus intervention) difference in mean NRS pain score change does not cross the non-inferiority margin of −1.0. If non-inferiority of an intervention arm to the comparator arm can be confirmed, superiority analysis for the difference in primary outcome will be performed using the respective two-sided 98.34% CI. Superiority can be claimed if the lower bound of the two-sided 98.34% CI for the between-groups difference in mean NRS pain score change lies above zero. Since this approach concerns a hierarchical closed-testing procedure examining a single confidence interval, statistical adjustment of the overall type I error is not required [34].

The secondary endpoint involving changes in NRS pain score at 20 min will be included in the mixed effect model. Statistical methods for other secondary outcomes will be specified in a detailed statistical analysis plan, which will be completed before database lock and unblinding of treatment allocation. Secondary endpoints use conventional two-tailed hypothesis tests and two-sided 95% confidence intervals. Assuming normality, continuous variables will be presented as mean with SD or the applicable confidence interval. When non-normally distributed, continuous variables will be presented

as median with interquartile range. Categorical variables will be presented using counts with percentages.

Interim analyses {21b}

No interim analysis will be performed. Since all study arms are standard of care for prehospital treatment of traumatic pain, futility of any treatment arm is not expected. Since both investigational medicinal products have a well-known safety profile, an interim analysis for safety reasons is not required.

Methods for additional analyses (e.g., subgroup analyses) {20b}

Subgroup analysis including all subjects that received paracetamol and/or diclofenac will be performed to evaluate the effects of co-administration of paracetamol and/or diclofenac on secondary outcomes.

Two exploratory analyses are planned due to their relevance to current practice:

1. Esketamine IV compared to esketamine IN; for subjects where fentanyl is contra-indicated, for example due to respiratory depression or hemodynamic instability.
2. Fentanyl IN compared to esketamine IN; for subjects where IV access is not available.

Only if both intervention arms are either superior or inferior to fentanyl IV (as determined in the primary analysis) will they be mutually tested using two-tailed hypothesis tests and an intention-to-treat population.

Any additional analyses will be specified in the statistical analysis plan, which will be completed before locking of the database and unblinding of treatment allocation.

Methods in analysis to handle protocol non-adherence and any statistical methods to handle missing data {20c}

Analysis will be performed based on the intention-to-treat and per-protocol principles to evaluate consistency of both analysis approaches compliant with recommendations for non-inferiority analyses [33]. The (modified) intention-to-treat population includes all patients that received at least one dose of study medication; the trial being double-blinded, the decision of whether or not to begin study treatment cannot be influenced by knowledge of the assigned medication and, therefore, the integrity of randomization (intention-to-treat principle) is preserved [35]. Moreover, the intervention being immediate, (nearly) all patients will receive at least one dose of the assigned study medication. The per-protocol population will exclude patients with major protocol deviations which may have an impact on the evaluation of the primary outcome; these will be defined in the statistical analysis plan before database lock and unblinding. In case of missing data, every attempt will be undertaken to retrieve the data. If the data are not retrieved, mixed models are capable of imputing missing outcome data based on the other variables that are included in the model. Methods will be detailed in the statistical analysis plan that will be completed before database lock and unblinding of treatment allocation.

Plans to give access to the full protocol, participant-level data and statistical code {31c}

(Meta)data will be shared according to the FAIR principle. Access to the full protocol, participant-level dataset and statistical code can be granted by the Principal Investigator if the purpose meets the criteria as described in the patient information folder.

Oversight and monitoring

Composition of the coordinating center and trial steering committee {5d}

The sponsor is responsible for study design, management, analysis and interpretation of data, writing of the report and the decision to submit the report for publication. The trial steering committee of the sponsor consists of five members with relevant (medical) expertise, including an emergency physician, an anesthesiologist-pain specialist and an anesthesiologist/Helicopter Emergency Medical Services physician. Two team members from the trial steering committee will provide day-to-day (organizational) support to the clinical trial site and local research personnel. Members of the trial steering committee will meet at least monthly to discuss trial conduct and progress. The trial site carries responsibility for performing the trial in line with the approved protocol and all applicable legislation and guidelines.

Composition of the data monitoring committee, its role and reporting structure {21a}

This trial is defined as a low-intervention trial under the EU Clinical Trial Regulation. Since this is a low-intervention trial where all study arms are standard of care and have well-known safety profiles, a data monitoring committee is not installed.

Adverse event reporting and harms {22}

This is a low-intervention trial where all study arms are standard of care. The investigational medicinal products are registered and have well-known safety profiles. Moreover, the trial takes place in an emergency setting with a heterogeneous study population and a limited timeframe. Recording all adverse events is therefore unfeasible. In accordance with Chapter 4.2 of "Risk proportionate approaches in clinical trials," only specific adverse

reactions that are of importance for the clinical applicability of the treatment arms are recorded [36]. Furthermore, all serious adverse events are recorded. Since all study arms are standard of care, EMS personnel are free to treat adverse events at their own discretion in accordance with EMS guidelines.

For this study, the adverse event recording period is defined as the period from patient recruitment up to arrival at the hospital. This is rational since our study focuses on the prehospital setting. Inclusion in our study is not expected to have consequences for in-hospital treatment, since side effects are generally short and transient.

Frequency and plans for auditing trial conduct {23}

Internal auditing is performed by an independent clinical research associate of the sponsor. The monitoring plan will be signed by the Principal Investigator before start of the recruitment period. The monitoring plan facilitates compliance with the Human Research Act (WMO), Good Clinical Practice (ICH-GCP) guidelines and ISO 14155. On-site monitoring visits are scheduled after every 100 randomized study subjects. Access to all trial-related documents including direct access to source data will be given at that time.

Plans for communicating important protocol amendments to relevant parties (e.g., trial participants, ethical committees) {25}

The sponsor will submit and obtain approval for substantial modifications to the original approved documents via the Clinical Trial Information System, the portal and database for all studies with medicinal products in the European Union/European Economic Area maintained by the European Medicines Agency. Following approval by the institutional review board, the Principal Investigator is responsible for notifying the clinical trial site. The revised protocol will be stored in the Investigator Site File. The modification will also be communicated through the trial registry, an update to the protocol manuscript and to the trial participants if relevant.

Dissemination plans {31a}

The results will be published in the trial registry (ClinicalTrials.gov, trial identifier: NCT0605122) and via publication in an international peer reviewed scientific medical journal. The investigator will inform the trial participants of the results of the study if they wish to be informed.

Discussion

This study aims to evaluate the efficacy and safety of esketamine IV, fentanyl IN, and esketamine IN compared with fentanyl IV for treatment of acute traumatic pain in adults in a randomized, controlled, double-blind non-inferiority trial. It has several strengths: first, this is one of few double-blind randomized controlled trials on analgesia in the prehospital setting. Second, this trial not only compares two analgesics (fentanyl and esketamine), but also two routes of administration (IV vs IN), which are all currently standard of care in prehospital practice. Consequently, the results of this trial have great relevance to prehospital care. Third, this trial is designed to minimalize the time until administration of analgesia. For example, EMS personnel receive ready-to-use syringes with study medication and deferred consent is applied. Finally, our sample size allows us to perform superiority analysis if non-inferiority of an intervention arm is confirmed.

This study also comes with challenges, mainly due to the prehospital emergency setting as previously described by Vianen et al. [37]. First, obtaining informed consent prior to participation is deemed impossible and deferred consent is applied in accordance with article 35 of the Clinical Trial Regulations. There is little practical experience with deferred consent among monitors and institutional review boards and extensive consultation with the privacy officer was required. Second, there are concerns about the quality of routinely collected prehospital patient data and the level of research experience in EMS is lower than in University Medical Centers. To improve data quality and protocol adherence, EMS personnel follow a study-specific training prior to the recruitment period. Third, emergency situations require fast assessment of pain. Since pain is multidimensional, the importance of multidimensional pain assessment has been recognized, including aspects such as cognition and functioning [38–40]. A pain measurement tool for prehospital use in emergency situations has specific requirements as such that it is simple, fast and does not require additional equipment [41]. The NRS pain score meets these criteria, is validated in acute pain and standard of care in Dutch prehospital practice and therefore appropriate for measuring the primary outcome [25, 42]. Fourth, there is a limited timeframe for follow-up, namely up until arrival the hospital, while prolonged (in-hospital) follow-up could also provide useful insights. Finally, it might be argued that the specific (side) effects of the investigational medical products jeopardize the double-blind nature of our study. However, earlier studies comparing fentanyl to ketamine in other populations found that blinding of care providers generally remains intact [23, 43]. To confirm these findings we have included a question where EMS personnel indicate which medicinal product they believe to have administered to the subject.

Trial status

Protocol version: 3

Date of recruitment start: 11 January 2024

Expected date of recruitment completion: 1 April 2026

Abbreviations

CRF	Case report form
EMS	Emergency medical services
GCP	Good clinical practice
IN	Intranasal
IV	Intravenous
NRS	Numeric Rating Scale

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13063-025-08869-9.

Additional file 1. WHO trial registration data set (version 1.3.1).

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Authors' contributions {31b}

MG is the executing investigator and contributed to study design and led the development of the protocol. NR is the clinical trial coordinator and contributed to study design and development of the protocol. JS is the local principal investigator of the clinical trial site and contributed to study design. MK is the trial pharmacist and contributed to the development of the protocol. MM is consultant-methodologist and contributed to the study design and development of the protocol. MH is the representative and principal investigator of the sponsor and contributed to study design. MR contributed to study design and development of the protocol. RW conceived the study, arranged funding and contributed to study design and development of the protocol. All authors read and approved the final manuscript.

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Data availability {29}

The final trial dataset is stored on a secured drive at the sponsor and available to the research team of the sponsor. This dataset can also be made available to others if this complies with the conditions for reuse as described in the patient information folder.

Declarations

Ethics approval and consent to participate {24}

The Institutional Review Board of the Amsterdam UMC has approved this trial. Informed consent is deferred until after arrival at the hospital, after which all subjects will be approached to provide informed consent, either electronically or written.

Consent for publication {32}

Not applicable.

Competing interests {28}

The authors declare that they have no competing interests.

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