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Published in:
Journal of Orthopaedic Reports

DOI:
10.1016/j.jorep.2024.100475

Publication date:
2025

Document version:
Final published version

JOREP 4 (2025) 100475

Contents lists available at ScienceDirect

Journal of Orthopaedic Reports

journal homepage: www.journals.elsevier.com/journal-of-orthopaedic-reports

The feasibility of perioperative methadone in older hip fracture patients: A pilot continual reassessment trial (MetaHip trial)☆,☆☆,☆☆☆

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ARTICLE INFO

Keywords:
Hip fracture
Older
Frail
Pain
Perioperative
Methadone
Continual reassessment method
Bayesian
Feasibility/pilot trial

ABSTRACT [1]

Background: Hip fractures cause extreme pain, primarily affecting the older and frail. The necessity of sufficient pain relief in combination with a lower tolerance for drugs makes the analgesic treatment of older patients difficult. A single dose of methadone might reduce postoperative pain and opioid consumption. However, the safety of using methadone for older and fragile patients is unknown.
Aim: Determine the maximal tolerable dose (MTD) of perioperative methadone in older hip fracture patients and assess the feasibility of this protocol for future clinical trials.
Methods: Hip fracture patients ≥60 years old were consecutively included at the hospital in the winter/spring of 2023. An adaptive algorithm allocated 0.10 mg/kg, 0.15 mg/kg, or 0.20 mg/kg of methadone to each patient, administered intravenously at the induction of anesthesia. The primary outcome was respiratory depression, which was monitored continuously. Occurrence required a dosage decrease, while absence allowed an increase. Registered Nurses at the orthopedic ward collected data using observation charts completed 6, 24, and 72 hours after surgery. Secondary outcomes include time spent in the post-anesthesia care unit (PACU), verbal rating pain score (VRS), opioid consumption, and nausea/vomiting.
Results: 30 patients completed the study. Nine received 0.10 mg/kg, and 21 received 0.15 mg/kg. Three patients experienced respiratory depression in PACU, all receiving 0.15 mg/kg methadone and undergoing general anesthesia. None of the spinal anesthesia patients or those receiving 0.10 mg/kg experienced respiratory depression.
Conclusion: Methadone is an effective analgesic for hip fracture surgery. The data suggests that the maximal tolerable dose of methadone in older hip fracture patients is 0.10 mg/kg. This study proves the feasibility of our trial setup and provides a foundation for future randomized controlled trials. Additionally, the findings suggest that the tolerability of methadone may vary depending on the type of anesthesia used, which merits further investigation.

1. Introduction [2 + 3]

1.1. Background/rationale

Danish hospitals treat 8.000 hip fracture patients every year.[1] The

☆ **Responsible ethics committee** Danish National Center for Ethics Ørestads Boulevard 5, Building 37K, ground floor 2300 Copenhagen S, Denmark Protocol number: 2209432 Date of approval: 02-08-2022.☆☆ The present paper conforms to the STROBE statement for reporting cohort studies. The numbers in brackets correspond to the item numbers from the checklist. The checklist can be found in supplementary materials.☆☆☆ Eudract: 2022-001857-22, Clinicaltrials.gov: NCT05581901, Statistical Analysis Plan: https://doi.org/10.1016/j.conctc.2023.101228.

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https://doi.org/10.1016/j.jorep.2024.100475
Received 28 August 2024; Received in revised form 24 September 2024; Accepted 30 September 2024
Available online 4 October 2024

Abbreviations

CRM	Continual Reassessment Method
RN	Registered Nurse
DLT	Dose-limiting toxicity
PACU	Post-anesthesia care unit
ED	Emergency department
MTD	Maximal tolerable dose
PONV	Postoperative nausea and vomiting
VRS	Verbal Rating Scale
GA	General anesthesia
SA	Spinal anesthesia
REDCap	Research Electronic Data Capture
OPEN	Open Patient Data Explorative Network
OUH	Odense University Hospital

global incidence of hip fractures continues to rise with the expanding older population, making them a significant health issue worldwide.[2] Hip fractures cause severe pain and require adequate pain relief treatment.[2,3] However, patients who suffer hip fractures are typically older and more fragile, with the fractures occurring at a median age of 81. This reduces the capacity to tolerate analgesic drugs.[1,4] This demand for sufficient pain relief, along with a reduced tolerance for drugs, makes it challenging to provide analgesic treatment for older hip fracture patients. Furthermore, research indicates that commonly used opioids often lead to chronic usage and addiction.[5,6] Consequently, there is a high demand for better alternatives.

The analgesic properties of perioperative methadone have been the subject of several studies.[7–13] However, there is limited evidence about using methadone for older and fragile individuals. Methadone's long half-life makes it an attractive option for pain relief as it provides better daily coverage and requires fewer administrations.[8] Furthermore, methadone is primarily excreted through the bile, making it a safe option for patients with impaired kidney function.[14,15] Doses in the literature range from 0.10 mg/kg to 0.20 mg/kg and concern younger healthy patients.[7–13] Thus, the maximum dose for the older and fragile remains to be discovered.

In a novel attempt to identify this maximum dose, the present study utilized the Bayesian Continual Reassessment Method (CRM) to increase the dose of methadone during close monitoring of toxicity. Dose-limiting toxicity (DLT) was defined as respiratory depression, as this is a clear indicator of opioid toxicity. This adaptive model offers the advantage of making real-time adjustments if we observe a DLT.

1.2. Aim

This study aims to determine the maximal tolerable dose (MTD) of perioperative methadone in older hip fracture patients and to assess the feasibility of this protocol for future clinical trials.

1.3. Objectives

This study evaluates methadone's tolerability in terms of toxicity, side effects, and PACU stay duration in older hip fracture patients. It also examines its impact on postoperative pain management and opioid consumption.

1.4. Hypothesis

It was hypothesized that an increased dose of methadone would entail a higher risk of respiratory depression, side effects, and prolonged stay in the PACU. Additionally, it was proposed that the maximal tolerable dose is either 0.10 mg/kg, 0.15 mg/kg, or 0.20 mg/kg.

2. Methods

2.1. Study design [4]

The study's design is an interventional cohort study conducted as an adaptive platform trial. It is a non-controlled, single-blinded phase IV trial using the Bayesian CRM. Please refer to the published statistical analysis plan to further elaborate on this method.[16]

2.2. Setting [5]

The study was conducted at a University Hospital, specifically in the emergency and orthopedic departments. Between January 10, 2023, and March 21, 2023, patients with hip fractures were consecutively included in the study from the emergency department (ED). An orthopedic physician managed the screening and enrolment process.

2.3. Participants [6]

Patients with hip fractures were consecutively included in the study based on the following criteria:

Inclusion criteria.

1. Patients diagnosed with an acute hip fracture on x-rays in the ED (collum femoris fractures, pertrochanteric fractures, and subtrochanteric fractures, ICD-10-codes: DS720-722).
2. Age ≥60 years.
3. Patients must be able to ask for supplementary analgesics if needed and give informed consent.
4. Patients must read and speak Danish.

Exclusion criteria.

1. Polytrauma:
   - *Defined as multiple fractures or multi-trauma patients.*
2. Previous allergic reactions or hypersensitivity towards methadone hydrochloride or sodium chloride.
3. Health Conditions Preventing Treatment:
   - Chronic obstructive pulmonary disease (Gold classification C + D)
   - History of acute asthma attacks or atopic skin conditions
   - Cor pulmonale
   - Raised intracranial pressure or recent head injury
   - Pheochromocytoma
   - History of paralytic ileus
   - QT interval prolongation on ECG upon admission (≥500 ms)
   - Myasthenia gravis
   - Known liver disorders
   - Hypotension (<100 mmHg systolic blood pressure at admission)
4. Concurrent administration:
   - With MAO inhibitors or within two weeks of suspending treatment with these medicinal products.
   - Of sedatives, *e.g.*, Benzodiazepines or related drugs.
5. Inclusion in other studies.
6. Impaired cognitive function:
   - *e.g., dementia.*
7. Current drug addiction: *e.g., opioid addiction or intravenous addiction.*

Note: Female patients were not tested for pregnancy as they were ≥60 years old.

2.3.1. Patient recruitment

According to hospital protocol, every patient presenting with a hip fracture to the emergency department is evaluated by an orthopedic physician within 4 hours of arrival. During this initial consultation, the physician provides the patient with both oral and written information regarding the study. After a consideration period of 2 hours, the

orthopedic physician proceeds with the screening and enrollment procedures, ensuring that eligible patients are appropriately informed and enrolled in the study. Simultaneously, the physician plans the necessary surgical intervention for the hip fracture. The flowchart in Fig. 1 details each step of the recruitment process, including the number of patients lost at each stage, from initial consultation to final enrollment.

3. Variables and data sources [7 + 8]

3.1. Primary outcome

The main focus of the study was respiratory depression, defined as having a respiratory rate of less than ten breaths per minute and a peripheral oxygen saturation of less than 94 %, even with 4 L of oxygen per minute. As previously indicated, this was defined as the dose-limiting toxicity (DLT). Data was collected from observation charts completed by primary caregivers in the post-anesthesia care unit (PACU) and in the orthopedic ward. In the PACU, registered nurses (RNs) continuously monitored peripheral oxygen saturation and respiratory rate until patients were transferred to the ward. Respiratory depression was evaluated upon arrival at the orthopedic ward and at 6, 24, and 72 hours after surgery.

3.2. Secondary outcomes

The RNs at the orthopedic ward consistently completed observation charts, which were used for data collection. REDCap hosted at OPEN at OUH was utilized to manage the charts electronically. These observation charts were the data source for our secondary outcomes.

Length of stay at the PACU: The length of stay at the PACU was recorded in hours for each patient, sourced from observation charts completed by RNs. Discharge from the PACU adhered to national guidelines outlined by the Danish Society for Anesthesiology and Intensive Medicine (DASAIM). Patients were discharged based on meeting criteria related to peripheral oxygen saturation, arousal, and pain level or following assessment by an anesthesiologist.

Amount of antidote needed: The number of times an opioid-specific antidote (*e.g.*, Naloxone) was required was recorded. The data source

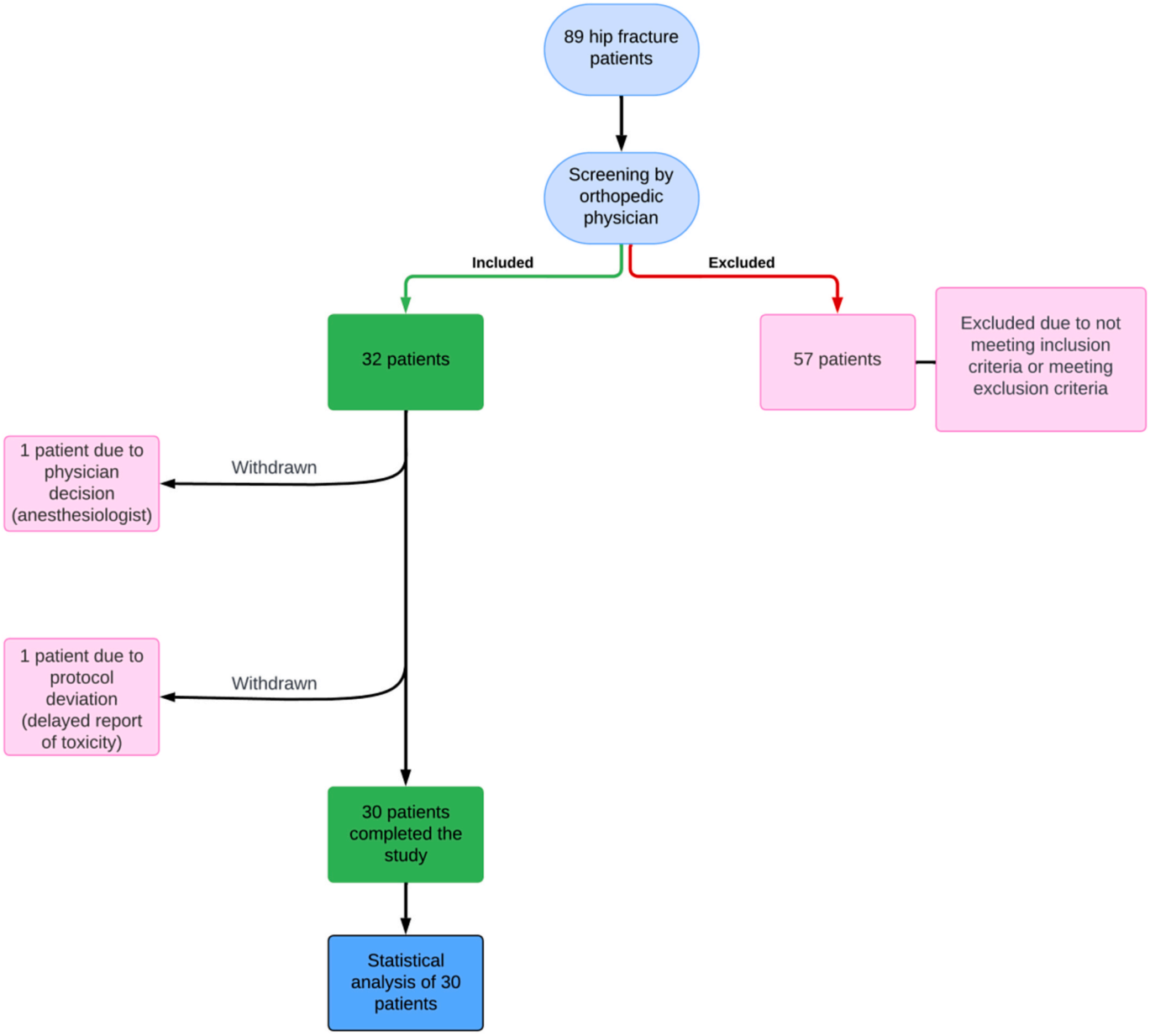

Fig. 1. Flowchart of the enrolment process. All patients lost at each step are reported.

was the observation charts filled in by the RNs at the orthopedic ward.

Postoperative opioid consumption: The mean consumption of rescue morphine equivalents for each group was recorded within specific time frames: Upon arrival and within the first 6, 24, and 72 hours after surgery. Morphine equivalent doses were calculated for various opioid types. The data source was the medical charts, with RNs recording the amounts on observation charts.

Opioid-related side effects: PONV was recorded binomial as present or not at 6 and 24 hours after surgery. The data source was the patient's statement, entered on the observation chart.

Postoperative pain assessment: Patients were asked to assess their pain intensity at the hip using the VRS, a validated scale for hip fracture patients.[17] The scale gives patients six choices; they must choose the one that best describes their pain. The choices are 0 (no pain), 1 (slight pain), 2 (moderate pain), 3 (severe pain), 4 (extreme pain), and 5 (unbearable/worst imaginable pain). They were asked to assess pain intensity upon arrival at the ward and 6, 24, and 72 hours after surgery. The data source was the patient's statement, entered on the observation chart.

3.3. Bias [9]

The assessment of pain is highly subjective, necessitating single-blinding in this trial. Patients are kept unaware of the methadone dose to prevent reporting bias. Another potential bias is that RNs on the ward might withhold rescue medication due to fear of inducing an opioid overdose. Thus, the RNs in the ward are also unaware of the exposure group. There is also a risk of reporting bias in the assessment of DLT, where occurrences might be overemphasized or underreported. However, in this trial, a certified RN anesthetist records DLT on a standard, non-trial-specific observation sheet. Additionally, the RN anesthetist is not involved in the study or patient treatment after they leave the PACU.

3.4. Study size [10]

The trial's sample size was calculated using the formula introduced by Kuen Cheung et al.[18]. Given the fragility of this population, the target toxicity level was defined as 0.10, with an accuracy of 0.6, and an odds ratio of 2. As a result, a sample size of 40 individuals would be adequate.

3.5. Intervention/exposure

Methadone hydrochloride was used as the investigational drug in this study. There were three exposure groups with dosages of 0.10 mg/kg, 0.15 mg/kg, and 0.20 mg/kg. Each patient's dosage was determined based on their total body weight, with weight measured in the emergency department when possible. If weight data were not available, self-reported weight was used.

The primary investigator allocated each patient to an exposure group, as detailed in the section *Treatment assignment*, and then calculated the individual dosage. An ED RN was responsible for preparing the investigational drug. The prepared syringe was placed beside the patient awaiting surgery at the infusion stand. The syringe did not specify the exposure group, ensuring only the preparing RN and the primary investigator knew the allocation. Ten minutes before incision, the investigational drug was intravenously administered with a single administration by the RN anesthetist, who remained unaware of the exposure group. Participants and RNs in the orthopedic ward were kept unaware of the exposure group, rendering this study single-blinded. A gradual upward titration of methadone was employed using the CRM, adjusting dosages according to the occurrence of DLT.[16] Refer to Fig. 2 for the flowchart depicting the allocation.

All patients received analgesic treatment according to the hospital guidelines. This included a preoperative peripheral nerve block (femoral nerve block), paracetamol (1g x4), a long-acting opioid (Contalgin 5mg x2), and a rescue opioid as needed. The investigational medicine was given in addition to standard care to confirm its safety when combined with other treatments. Epidurals are not routinely used in our region for this patient group as they can delay early mobilization and are not part of the standard treatment for hip fractures.

3.6. Statistical methods [11 + 12]

3.6.1. Descriptive statistics

Descriptive statistics was applied to provide an overview of the study population's baseline characteristics. Numbers are presented as means with standard deviation (normally distributed data) or medians with interquartile range (IQR; skewed data). An unpaired *t*-test or Mann-Whitney *U* test was applied to test for mean or median differences between the groups, according to the distributional pattern of the data. Fisher's exact or χ^2 tests were performed to assess statistical differences in the proportions of categorical features. All analyses use a significance level of 0.05 and 95 % confidence intervals (CIs).

3.6.2. Primary analysis

This trial uses the Bayesian CRM. Please refer to the published statistical analysis plan to further elaborate this method.[16] The stopping guidelines and probabilistic priors are briefly summarized below.

- If 40 persons are included.
- If the probability of the lowest dose exceeding a predetermined toxicity threshold (set at 0.10) is greater than 95 % and more than ten persons are included.

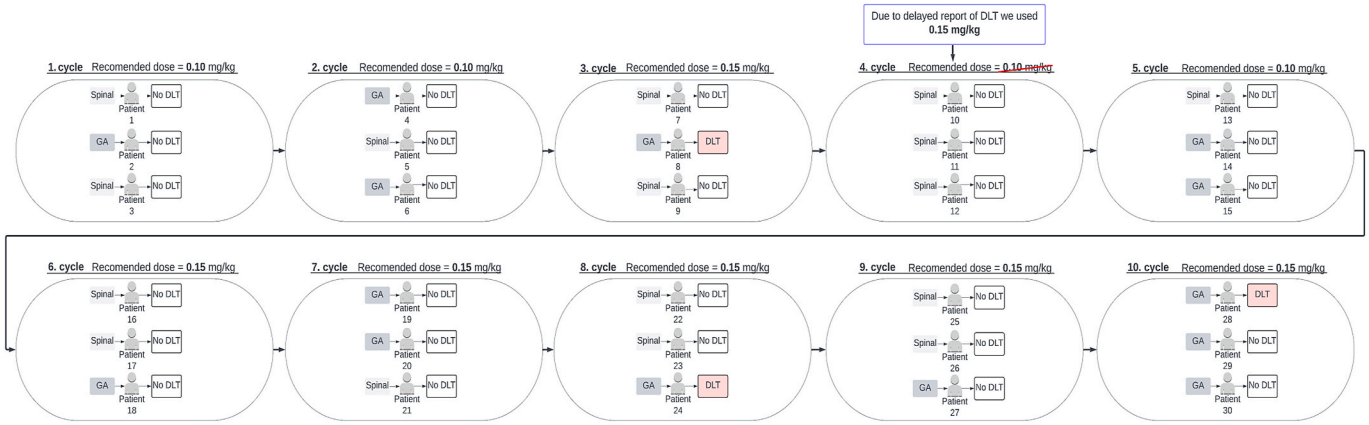

Fig. 2. Flowchart illustrating the cycles of treatment assignment. DLT = Dose Limiting Toxicity (i.e., respiratory depression), general anesthesia, Spinal = spinal anesthesia, recommended dose = the dose suggested by the algorithm when running our script in R studio.

- If the 95 % credibility interval of the toxicity level for the MTD is between 0 and 0.10 and at least ten patients are included, or the width of the 95 % credibility interval is smaller than 20 points.
- If all the above is true with ten participants included.

Note: The predetermined toxicity threshold of 0.10 is clinically acceptable and significantly lower than the approximately 0.24 reported in the literature.[19] The point estimate of the toxicity for the maximum tolerated dose (MTD) must remain below 0.10. Additionally, 0.24 serves as a critical threshold, which the 95 % credibility interval for the MTD must fall below. An incidence of 0.24 was reported for elective total hip arthroplasty,[19] suggesting that the incidence is likely higher when treating older, frailer patients undergoing acute surgery. Consequently, an estimated risk of toxicity below 0.10 with a confidence interval below 0.24 is acceptable.

3.6.3. Treatment assignment

The orthopedic doctor would notify the primary investigator when a patient was included. The primary investigator would then assign each patient to a methadone group (0,10 mg/kg, 0,15 mg/kg, or 0,20 mg/kg) using the model-based CRM in R Studio.[16] This method used registered primary outcomes from the previously included patients or the pre-specified prior if no data had been collected. It would assign patients in cycles of three patients at a time. The algorithm would initially assign the lowest dose and would start escalating the dose when the width of the 95 % credibility interval was approaching 20 %-points. Based on the posterior estimates and prior input, the algorithm would keep escalating the dose if the expected toxicity did not exceed 0.1. See Fig. 2 for a flowchart of the treatment assignment or a copy of the script used in R studio in the supplementary materials.

3.6.4. Secondary analyses

The analysis of the secondary outcomes consists of the following.

- *Length of stay at the PACU*: Survival analysis was employed to present the length of stay at the PACU graphically. Kaplan-Meier curves, along with pseudo-observations, were applied for visual presentation only. A linear regression analysis investigated potential differences in PACU stay duration among the dose levels.[20] Bootstrapped confidence intervals were applied in our linear regression model.
- *Amount of antidote needed:* The limited number of observations precluded the possibility of conducting meaningful statistical analysis.

Postoperative opioid consumption: Due to the integer-like nature of the administered dosage, a negative binomial regression was used. Clustered standard errors were applied on the patient ID level, as the variation distribution within subjects was deemed non-reproducible. The mean consumption of rescue morphine equivalents from each group was used in the calculations.

- *Opioid-related side-effects*: The intended model was not estimable due to the limited number of observations. Consequently, Fisher's exact test was employed to examine the relationship between methadone dose and complications.
- *Postoperative pain assessment:* Postoperative pain was analyzed using a linear mixed effect model with bootstrapped confidence intervals, no covariates, and participants as random effects. The global p-value was used to minimize issues with multiple testing. The original Likert scale was used for interpretation: 0 (no pain), 1 (slight pain), 2 (moderate pain), 3 (severe pain), 4 (extreme pain), and 5 (unbearable/worst imaginable pain).

Note: Effect modification by time was assessed in the analyses with repeated measurements by likelihood-ratio tests, and it was present only in the opioid consumption analysis. Parametric model assumptions were evaluated graphically in residual and quantile-quantile plots. If the distributional assumptions were false, bootstrapped confidence intervals were used in the models. STATA 17, StataCorp. 2023 was used to conduct the statistical analyses. Please see the statistical analysis plan for the strategy regarding the statistical analysis.[16] Any deviations from the plan will be elucidated.

4. Results

4.1. Participants [13]

From 10 to 01–2023 to 21-03-2023, 89 hip fracture patients were screened for inclusion at the hospital. 32 patients were confirmed eligible and included in the study. Nine patients received 0.10 mg/kg (5 patients in general anesthesia and 4 in spinal anesthesia), and 21 received 0.15 mg/kg (9 in general anesthesia and 12 in spinal anesthesia). One patient received 0.20 mg/kg by mistake, as the report of DLT, unfortunately, was delayed for the patient prior. Thus, the algorithm changed the dose to 0.15 mg/kg when the occurrence of a DLT was included (see Fig. 2). The trial continued using 0.15 mg/kg and never reached 0.20 mg/kg again. Another patient was withdrawn per the request of the attending anesthesiologist. The statistical analyses disregard the patient receiving 0.20 mg/kg and the patient withdrawn by the anesthesiologist (see Fig. 1).

Ten correct cycles of treatment assignment were executed throughout the study, ignoring the incorrect one. See Fig. 2 for a flowchart of the treatment assignment. Stopping rule no. 3 (see *Statistical methods → Primary analysis*) was triggered when 30 patients had been included, and the inclusion of further patients stopped immediately. The stopping rule was triggered because the 95 % credibility interval of the toxicity level for the 0.10 mg/kg group was smaller than 20 points, and more than ten patients had been included.

4.2. Descriptive data [14]

Descriptive statistical analyses were conducted on the patient cohort, confirming its similarity to critical demographics and clinical factors in the general population. The mean age was 82, and 37 % were male. Furthermore, as shown in Table 1, no significant differences were found in the population characteristics between the exposure groups.

4.3. Outcome data [15 + 16]

4.3.1. Primary outcome data

4.3.1.1. Dose-limiting toxicity (DLT). In the study, three cases of DLT, i.e., respiratory depression, were observed. They were all in the 0.15 mg/kg exposure group, and all underwent general anesthesia. Participants who underwent spinal anesthesia in the 0.15 mg/kg group did not manifest any instances of DLT (see Fig. 2 for flowchart). The mean posterior estimate of toxicity for 0.10 mg/kg = 0.07 (± SD 0.04, CI 0.02; 0.17), 0.15 mg/kg = 0.13 (± SD 0.06, CI 0.04; 0.26), and the predicted estimate for 0.20 mg/kg = 0.19 (± SD 0.07, CI 0.08; 0.35). Thus, 0.10 mg/kg is the only dose with an estimated toxicity below our cut-off toxicity of 0.10 and a 95 % credibility interval below the clinical practice level of 0.24. Fig. 3 shows the distribution of participants and DLT. Fig. 4 visualizes the estimated posterior probability of DLT for the different doses**.** Every instance of DLT occurred in the PACU within a few hours of methadone administration. No cases of DLT occurred later than 3 hours after administration of methadone.

4.3.2. Secondary analyses

- *Length of stay at the PACU*: Patients with 0.15 mg/kg methadone had a 0.34-h (CI -1.48; 0.89) shorter stay at PACU, which was statistically insignificant (p = 0.62). The results are visualized in Fig. 5.

Table 1
This is a table illustrating the demographic data from study participants. There are no significant differences between the participants in each exposure group. The numbers in parenthesis indicate the percentage of the total number of participants in the specific group.

Table 1: Population characteristics

	Total	0.10 mg	0.15 mg	p-value
	N = 30	N = 9	N = 21	
Fracture type				0.77
Collum femoris fracture	21 (70 %)	6 (67 %)	15 (71 %)	
Pertrochanteric fracture	8 (27 %)	3 (33 %)	5 (24 %)	
subtrochanteric fracture	1 (3 %)	0 (0 %)	1 (5 %)	
Age	82[8]	83[9]	82[8]	0.83
Gender (male)	11 (37 %)	3 (33 %)	8 (38 %)	1.00
ASA				0.37
2	13 (43 %)	3 (33 %)	10 (48 %)	
3	16 (53 %)	5 (56 %)	11 (52 %)	
4	1 (3 %)	1 (11 %)	0 (0 %)	
BMI	24[4]	24[3]	24[4]	0.57
Smoking	5 (17 %)	0 (0 %)	5 (24 %)	0.29
Alcohol consumption				0.59
0/week	11 (37 %)	2 (22 %)	9 (43 %)	
<10/week	18 (60 %)	7 (78 %)	11 (52 %)	
>10/week	1 (3 %)	0 (0 %)	1 (5 %)	
Heart failure	4 (13 %)	1 (11 %)	3 (14 %)	1.00
Arrhythmia	9 (30 %)	4 (44 %)	5 (24 %)	0.39
Peripheral arterial disease	4 (13 %)	0 (0 %)	4 (19 %)	0.29
Hypertension uncomplicated	17 (57 %)	6 (67 %)	11 (52 %)	0.69
Other neurological disorders	4 (13 %)	2 (22 %)	2 (10 %)	0.56
Diabetes uncomplicated	5 (17 %)	1 (11 %)	4 (19 %)	1.00
Diabetes complicated	1 (3 %)	0 (0 %)	1 (5 %)	1.00
Hypothyroidism	2 (7 %)	1 (11 %)	1 (5 %)	0.53
Renal failure	1 (3 %)	0 (0 %)	1 (5 %)	1.00
Malignancies	1 (3 %)	1 (11 %)	0 (0 %)	0.30
Osteoporosis	4 (13 %)	1 (11 %)	3 (14 %)	1.00
Chronic opioid use	1 (3 %)	0 (0 %)	1 (5 %)	1.00

Amount of antidote needed: The limited observations precluded meaningful statistical analysis. Only one patient received an antidote, accounting for two out of the 120 possible observations.

- *Postoperative opioid consumption:* Participants in the 0.15 mg/kg group had a higher mean rescue morphine equivalent consumption, but this was statistically insignificant IRR 72h = 1.19 (CI 0.69; 2.07, p = 0.38). The complete analysis is shown in Table 2 and visualizes the consumption over time in Fig. 6. A third of the enrolled patients required no rescue medication throughout their hospital stay. The mean consumption of rescue morphine equivalent within the first 72 hours was 9.4 mg in the 0.10 mg/kg group and 12.6 mg in the 0.15 mg/kg group.

Opioid-related side effects: The group administered with 0.10 mg/kg showed PONV in 9.1 % of our observations, whereas the 0.15 mg/kg group exhibited PONV in 9.8 % of the observations. Consequently, the analysis did not detect any notable variance in the occurrence of PONV between the groups (p = 1.00), indicating no statistically significant difference.

- *Postoperative pain assessment:* Although the postoperative pain scores of patients receiving 0.15 mg/kg were 0.08 points lower on average on the original Likert scale (CI -0.28 to 0.11), this difference was not statistically significant (p = 0.41). There were 105 successful responses, and 15 responses were missing. 0 (no pain) accounted for 59 of the responses, 1 (slight pain) accounted for 36, and 2 (moderate pain) accounted for only 10. There were no responses higher than 2 (moderate pain).

4.4. Other analyses [17]

4.4.1. The influence of anesthesia

Every instance of DLT was observed within the 0.15 mg/kg dosage group. However, all individuals who exhibited DLT had another common factor: they had undergone general anesthesia (GA). Conversely, participants who underwent spinal anesthesia (SA) while receiving the same 0.15 mg/kg methadone dosage (n = 12) did not manifest any instances of DLT. Hence, it seems that the choice of anesthesia can affect a patient's ability to tolerate opioids, making them more prone to developing respiratory depression when using general anesthesia. Another possibility is confounding by indication where patients receiving SA are less frail and hence are less likely to experience respiratory depression. Further research is needed to elaborate on this.

During the statistical analyses, it was assessed whether anesthesia type (GA or SA) significantly modified other parameters, i.e., postoperative opioid consumption. No statistically significant difference was found. As a result, the data from both GA and SA patients are combined for this study.

While the data did not reveal any significant anesthesia-related effect modification, the sample size might be too small, making the analysis underpowered. Consequently, stratified randomization or separate analyses are recommended in future trials investigating perioperative methadone.[21]

5. Discussion

5.1. Key results [18]

The data indicate that the MTD is 0.10 mg/kg. Administration of 0.15 mg/kg did not demonstrate significant advantages. Specifically, no statistically significant differences were observed in critical parameters, including duration of stay in the PACU, postoperative opioid

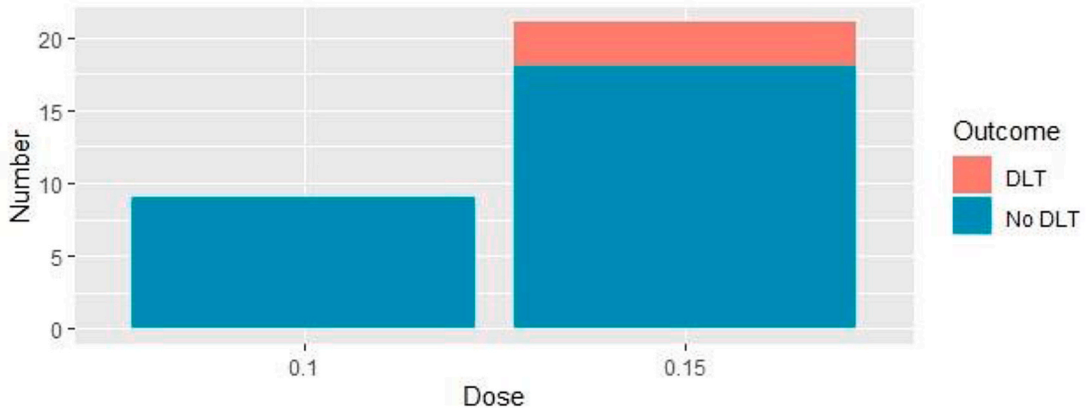

Fig. 3. Number of participants and cases of DLT in each exposure group.

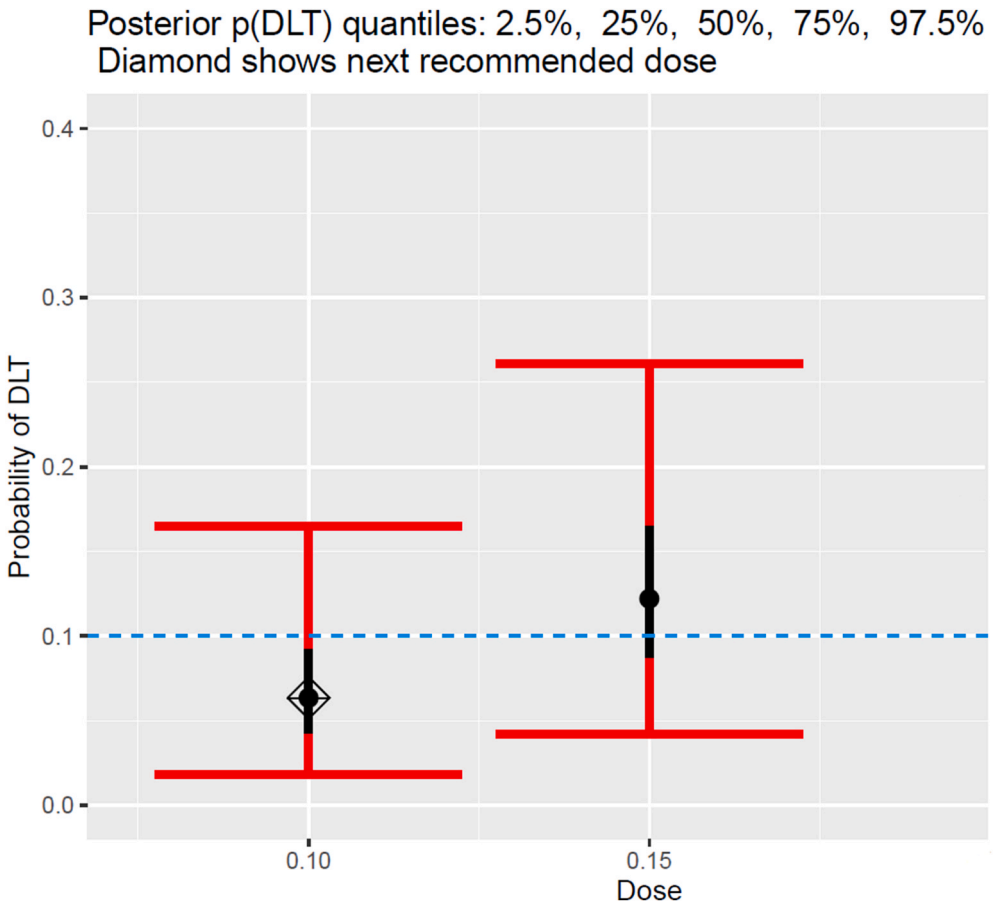

Fig. 4. The estimated probability of DLT for each dose is illustrated with 95 % credibility intervals. The blue dotted line indicates our target toxicity of 0.10. The black diamond is the estimated toxicity for the 0.10mg/kg dosage below 0.10. The credibility interval for 0.10 mg/kg dosage is also below 0.2. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

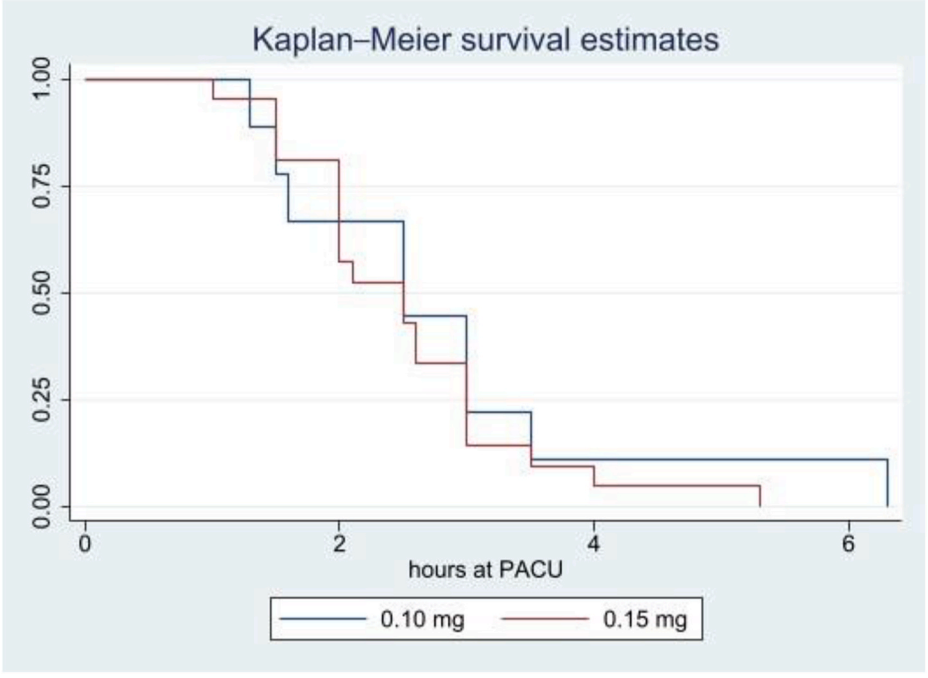

Fig. 5. Kaplan-Meier curve visualizing the length of the stay at PACU for each dose.

Table 2
The calculated Incident Risk Ratio (IRR) for opioid consumption at the respective time points shows no statistically significant difference between the exposure groups (p = 0.34).

Postoperative Opioid Consumption (in mg)				
Outcome	Covariate	Time point	IRR (95 % CI)	p-value
Opioid consumption	0.15 mg/kg	baseline	1.35(1.01; 1.82)	0.34
Opioid consumption	0.15 mg/kg	6 hrs	0.99(0.75; 1.31)	
Opioid consumption	0.15 mg/kg	24 hrs	0.98(0.76; 1.26)	
Opioid consumption	0.15 mg/kg	72 hrs	1.11(0.88; 1.4)	

*reference category: 10 mg/kg group.

consumption, postoperative pain levels, antidote requirement, or occurrence of PONV. The secondary analyses may be underpowered due to a small sample size (n = 30). However, the risk of DLT is higher with the 0.15 mg/kg dosage, where the estimated toxicity exceeds 0.10, and the 95 % credibility interval exceeds the clinical practice level of 0.24. Based on these findings, this study concludes that the MTD for this specific patient group is 0.10 mg/kg.

This MTD differs from similar studies of 0.15 mg/kg – 0.25 mg/kg.[22,23] However, the studies in the literature focused on younger, healthier patients undergoing elective surgery, whereas this trial investigated older, frail patients undergoing acute surgery. Thus, a lower MTD for these patients was anticipated. The findings highlight the importance of customizing dosage regimens to suit distinct patient populations. The methodologies presented in this paper can serve as a valuable tool for streamlining and enhancing the precision of future dose adjustments, offering a straightforward and dependable approach.

6. Limitations & strength [19]

Employing the CRM made it possible to explore various doses with a minimal number of participants. This approach is particularly advantageous given the frailty of the target patient population. This innovative dose-adjustment method can pave the way for future research. One limitation of this trial is the relatively small sample size (n = 30). Consequently, this study differs from traditional safety trials, and the safety of methadone usage remains an ongoing discussion.[7,8,10–12,14,15,26] Instead, this trial investigated methadone use within a specific patient population, specifically focusing on the older and frail. When administering 0.10 mg/kg of methadone, the resulting estimate of toxicity falls below the target toxicity level of 0.10, indicating a favorable safety profile. However, it is worth noting that the 95 % credibility interval extends beyond 0.10, reaching 0.17. Despite this, the upper limit of the interval remains below the clinical practice level of 0.24.[19] Because the credibility interval crosses 0.10, it is not possible to conclusively rule out relevant toxicity. However, since the point estimate is below the predefined cut-off of 0.10 and the upper bound of the credibility interval remains well below the clinical practice level of 0.24, the findings support the viability of perioperative methadone in this patient population.

7. Interpretation [20]

In addition to suggesting the MTD, the statistical analyses uncovered promising analgesic properties of perioperative methadone. All participants consistently reported low pain scores (no pain or slight pain), unaffected by methadone dosage. The mean consumption of rescue morphine equivalents within the first 72 hours of 9–12 mg was very low compared to the usual 30–40 mg stated in the literature.[24,25]

Nevertheless, evaluating perioperative methadone against a conventional analgesic regimen is beyond the scope of this feasibility study. This trial advocates for the potential of perioperative methadone to enhance analgesic treatment for older hip fracture patients and calls for further research on this subject.

8. Generelizability [21]

The incorporation of both general anesthesia (GA) and spinal anesthesia (SA) into the study enhances its applicability. Additionally, allowing participants to receive peripheral nerve blocks and standard

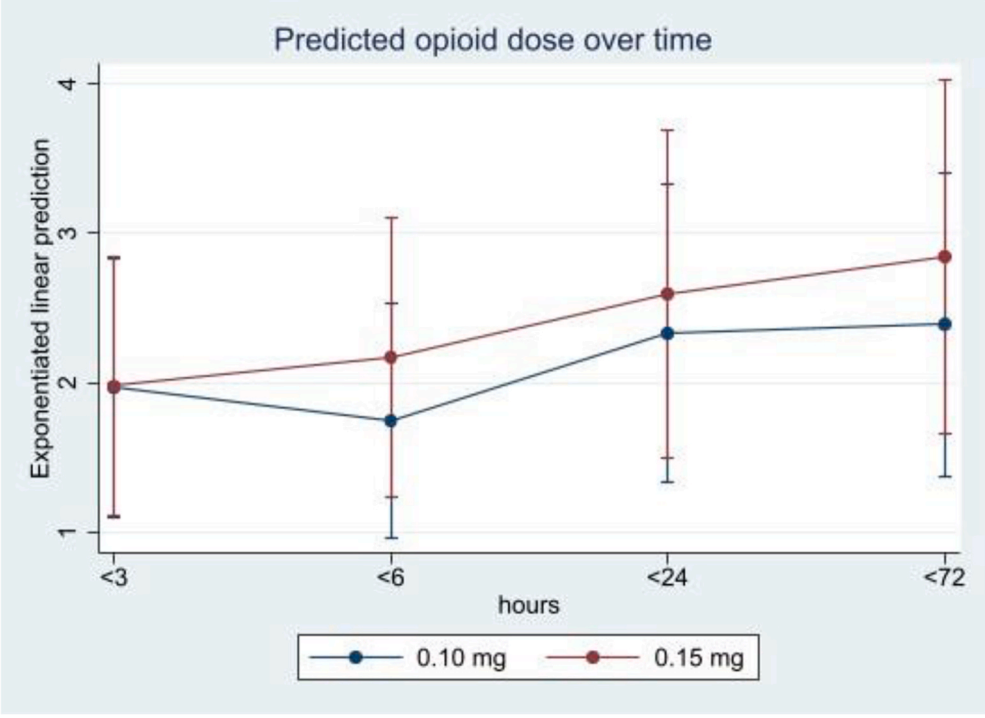

Fig. 6. Graph visualizing the mean consumption of rescue morphine equivalents at the different time points for the two groups. The y-axis represents milligrams of morphine equivalents, and the x-axis represents time in hours.

analgesic regimens further bolsters its generalizability. The descriptive statistics show a close resemblance between study participants and the broader patient population, indicating that the selected group represents a more comprehensive range of patients. This alignment was achieved through minimal exclusion criteria and the inclusion of various hip fracture types. The study's setting demonstrates a high generalizability, facilitating easy comparison with typical Western hospitals. Furthermore, the study methods were published on clinicaltrials.gov and the statistical methods were published in a statistical analysis plan[16] prior to patient inclusion. This ensures transparency and reproducibility.

9. Conclusion

The findings suggest that 0.10 mg/kg is the maximum tolerated perioperative methadone dose for older hip fracture patients. This conclusion considers the observed risk of dose-limiting toxicity (DLT) and several critical parameters in this trial. The estimated risk of toxicity was below 0.10 in this group only, and although the confidence interval crosses 0.10 (0.02; 0.17), it remains below the clinical practice level of 0.24, indicating an acceptable level. This study demonstrates the feasibility of the trial setup and provides a foundation for future randomized controlled trials.

Funding [22]

The study is non-commercial. External grants from The A.P. Møller and Chastine Mc-Kinney Møller Foundation (grant number L-2022-00365) and Knud and Edith Eriksens memorial foundation (grant number 62786–2023) cover running costs. Scholarships from the Region of Southern Denmark (grant number 22/26,251) and University Hospital of Southern Denmark (grant number 22/25,256) cover the salary of the study investigator. Thus, the financing did not affect study completion, results or publication.

Ethical approval and patient consent

The present study was conducted according to ethical standards outlined in the Helsinki II declaration, the Danish Health Act, and The Act on Processing Personal Data. Approval from the Danish Data Protection Agency (case number 22/29376), The Danish National Research Ethics Committee (case number 2209432), and the Danish Medicine Agency (case number 2022101827), was obtained before enrolling any patients. The study protocol was registered on clinicaltrials.gov (identifier NCT05581901), and the statistical analysis plan was published before its completion, following standard transparency measures.[16]

Declaration of patient consent form

Patient inclusion adhered to the subjects' rights outlined by the National Committee on Health Research Ethics. Participants were thoroughly informed about potential risks and corresponding mitigative measures following ethical guidelines on informed consent. After a deliberation period of 2 hours, the orthopedic doctor obtained both oral and written informed consent before inclusion. Orthopedic doctors conducted recruitment and information dissemination. Importantly, participants retained the right to withdraw consent without impacting their treatment or overall quality of care. Our inclusion procedure aligns with practices in studies involving similar patient groups.[27]

Financial support and sponsorship

The study is non-commercial. We did not receive financial support or sponsorships; any funding came from external grants or scholarships.

Disclosures

All authors declare no conflict of interest. Study personnel and site had no economic interests in completing the study. The study was noncommercial.

Ethical statement

The present study adhered to ethical standards outlined in the Helsinki II declaration, the Danish Health Act, and The Act on Processing of Personal Data. Prior to enrolling patients, we obtained approval from the Danish Data Protection Agency (case number 22/29376), The Danish National Research Ethics Committee (case number 2209432), and the Danish Medicine Agency (case number 2022101827). In accordance with transparency measures, we registered the study protocol on clinicaltrials.gov with the identifier NCT05581901 and published the statistical analysis plan before completing the statistical analysis.

14. CRM script for R studio

```
install.packages("bcrm", dependencies = TRUE)
install.packages("rjags", dependencies = TRUE)
library(bcrm)
library(rjags)
dose < - c(10, 15, 20)
p.tox0 <- c(0.050, 0.3, 0.80)
target.tox < - 0.10
sdose < -log(dose/250)
Power.LN.bcrm < - bcrm(stop = list(nmax = 40, precision = c
(0,0.2)), sdose = sdose.
dose = dose, ff = "logit1″, target.tox = target.tox, prior.alpha = c
(1,0.25,1)
constrain = FALSE, pointest = "mean", method = "rjags")
```

Credit authorship contribution statement

Kevin Heebøll Nygaard: Study investigator, member of the research group, involved in the planning and conduction of the study, involved in the interpretation of data, and constructed the first draft of the manuscript in collaboration with the co-investigator and lead biostatistician.

Lasse Eriksen: Co-investigator, constructed the first draft of the manuscript in collaboration with the study investigator and lead biostatistician. Involved in conduction of the study.

Thomas Strøm: Member of the research group, involved in the planning of the study, involved in data interpretation and revised the work.

Kirsten Specht: Member of the research group, involved in the planning of the study, involved in data interpretation and revised the work.

Sofie Ronja Petersen: Lead biostatistician, involved in the planning of the study, constructed the first draft of the manuscript in collaboration with the study investigator and co-investigator, and contributed substantially to the statistical plan and data management.

Jesper Ougaard Schønnemann: Chief investigator and head of the research group, involved in the planning and conduction of the study, involved in data interpretation and revised the work.

Generally: All authors contributed with scientific knowledge. All authors revised the work and approved the final manuscript.

Declaration of competing interest

The corresponding author and co-authors declare no conflict of interest.

Acknowledgement

We thank the various departments for their valuable collaboration during the study, explicitly acknowledging the Department of Orthopedics, the Emergency Department, and the Department of Anesthesiology and Intensive Care. Additionally, we extend our appreciation to the personnel within the clinical research department for their professional guidance and support.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jorep.2024.100475.

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