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Clinical Trial Protocol

CLINICAL TRIAL PROTOCOL

A double-blind, randomised, placebo-controlled trial comparing intrathecal bupivacaine with bupivacaine plus morphine to reduce delirium in patients with hip fractures—Salmon-Mind trial study protocol

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Abstract

Background: Surgical treatment of proximal femur fractures is complicated by postoperative delirium in about one-third of patients. Pain and opioid consumption are modifiable factors that may influence the incidence of delirium.[1] An intrathecal injection of morphine may lead to a reduction in postoperative pain and reduced systemic opioid consumption. In current practice, the addition of morphine to intrathecal anaesthesia is commonly used but depends on the anaesthesiologist's preference. Recently, a retrospective study found that intrathecal morphine was independently associated with a lower incidence of delirium. However, this has to be confirmed in a prospective, randomised study. We hypothesise that using intrathecal morphine reduces postoperative pain and opioid consumption during the first 48 h after surgery and reduces the incidence of delirium during hospital admission. We also seek additional evidence of the association between neuronal injury (delirium) and neurofilament light in serum of patients with proximal femur fractures.

Objective: The primary objective is to compare the incidence of delirium. The secondary objectives are to compare pain scores, systemic opioid consumption, and (opioid-related) side-effects. The tertiary objective is to test the association between intrathecal morphine and neurofilament light as a marker of neuronal injury.

Study design: A double-blind, randomised, placebo-controlled intervention study is proposed.

Study population: All patients with a proximal femur fracture who are scheduled for surgery under spinal anaesthesia.

Intervention: The intervention is the addition of morphine 100 μg to the intrathecal injection for spinal anaesthesia. The intervention group will receive a mixture of bupivacaine 10 mg and morphine 100 μg. The control group will receive bupivacaine 10 mg.

Clinical trial registration: EU Clinical Trials Register: EudraCT number 2020-002143-27.

Keywords: delirium; femur fracture; frailty; intrathecal morphine

Although the incidence of postoperative delirium in hip fracture patients can be decreased by 40% using a multidisciplinary approach, it is still a common complication in the fragile population.[1] It is associated with increased mortality, prolonged admission time, the inability of patients to return to their usual residence, and impaired functional recovery. Moreover, the

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occurrence of postoperative delirium is a predictor of cognitive impairment and dementia.[2,3] Amongst the modifiable factors influencing the incidence of postoperative delirium are pain and systemic opioid use.[4,5] Pain and systemic opioid use can be decreased by administering intrathecal morphine, which provides adequate analgesia for 24–48 h.[6] Consequently, intrathecal morphine could reduce the prevalence of postoperative delirium in patients with a proximal femoral fracture.

Intrathecal administration of morphine is a commonly used method of analgesia for various types of surgery[1,7,10–14] including proximal femoral fractures,[6] but its use depends on the anaesthesiologist's preference. More widespread use may be limited because of potential side-effects, such as pruritus, nausea, and late respiratory depression. One small randomised study investigated intrathecal morphine in proximal femoral fracture patients and observed less pain in patients who received intrathecal morphine.[8] Delirium was not investigated in that study. A recent observational study showed a decreased incidence of delirium in patients who received intrathecal bupivacaine and morphine *vs* patients who received intrathecal bupivacaine alone (5.9% *vs* 19.7%, P=0.046).[9] In all available studies, the sample size was small. Standard care did not include state-of-the-art treatment such as fascia iliaca compartment block or pericapsular nerve group block.[1]

Considering this background, a randomised study to investigate the effect of intrathecal morphine on the incidence of delirium in patients with proximal femoral fracture surgery is warranted. We hypothesise that intrathecal morphine reduces pain and postoperative systemic opioid use, thus reducing the incidence of delirium.

Additionally, this study will investigate the serum concentration of neurofilament light (NFL) as a marker of neuronal injury and correlate it with the occurrence of delirium for future screening and evaluation of treatment. NFL is reported to be a biomarker for delirium.[15] Serum concentration increases until postoperative day (POD) 2.[16] Therefore, we will take serum samples for NFL preoperatively and on POD 2. Patients with dementia already have higher concentrations of serum NFL, which complicates the interpretation. The NFL measurement aims to investigate the correlation between NFL increase and delirium.

Objectives

The primary objective is to investigate if adding intrathecal morphine to the spinal anaesthetic during proximal femoral fracture surgery affects the incidence of delirium during admission. Secondary objectives are to investigate postoperative pain, systemic opioid consumption, side-effects (i.e. nausea, pruritus, respiratory depression, urinary retention), length of hospital stay, discharge facility, and mortality. A tertiary objective is to investigate the serum concentration of NFL in a subset of the patients and correlate it with the incidence of delirium.

Study design

We will conduct a double-blind, randomised, placebo-controlled study. Recruitment to the study is planned for at least 2 yr at the Maasstad Hospital, Rotterdam, The Netherlands (Fig. 1). A substudy of the randomised trial is an

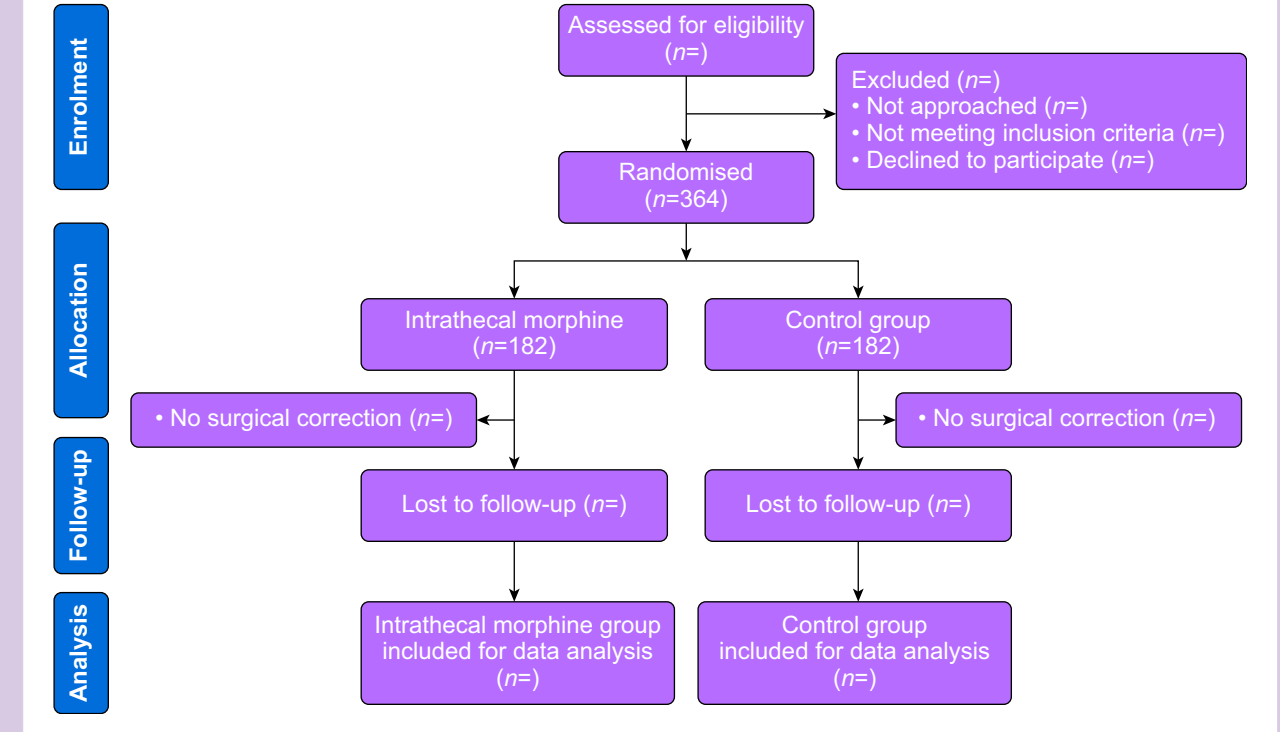

Fig 1. CONSORT flow diagram.

observational study investigating serum NFL concentration, delirium, and the influence of intrathecal morphine. This will only be performed in some of the study cohort.

Randomisation, blinding, and treatment allocation

All patients with proximal femur fracture will be screened for eligibility. They will receive verbal and written information before they give their informed consent. If they have a designated representative, the representative will receive verbal and written communication to provide informed consent on behalf of the patient. If the patient has delirium before the operation and they or their representative cannot give consent, the patient will be ineligible.

Patients will be randomly allocated into one of two groups; group SIM will receive spinal anaesthesia with bupivacaine and intrathecal morphine, and group SA will receive spinal anaesthesia with bupivacaine alone. The randomisation will occur in blocks of 20 to prevent an unequal distribution of groups over time. Randomisation will be performed by an independent person using closed opaque envelopes, only to be opened when the patient consents to participate in the study. If a serious adverse event occurs, an independent person will open the randomisation code to check for group allocation. The researchers and the patient will be blinded to treatment allocation. However, the attending anaesthesiologist and anaesthesia nurse will not be blinded for safety reasons. If an intrathecal injection is attempted but unsuccessful, the patient will remain in the study, and follow-up continued.

Study population

Population (base)

Patients will be scheduled for a surgical repair of a proximal femoral fracture in the Maasstad Hospital. Approximately 500 patients with proximal femur fractures are admitted to our hospital annually. It is anticipated that 50% of these patients will not qualify for the study and 30% will decline to participate, allowing for completion of the study in a little more than 2 yr (see sample size calculation below).

Inclusion criteria

To be eligible for participation in this study, a patient must meet all the following criteria:

- Proximal femoral fracture
- Scheduled for surgery
- Intrathecal anaesthesia is planned

Exclusion criteria

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

1) patients' refusal or patients incapable of making decisions regarding anaesthesia and when no legal representative is available.
2) contraindications to spinal anaesthesia:
   i) coagulation disorders (clopidogrel, international normalised ratio [INR] >1.8, anticoagulation with nadroparin (>100 antifactor Xa-IE kg^{-1}), heparin (activated partial thromboplastin time [APTT] >30 s), recent use of a direct oral anticoagulant, as stated in the guideline 'Neuraxisblokkade en antistolling' by the Dutch Society of Anaesthesiology
   ii) aortic valve stenosis of aortic valve area (AVA) <1.0 cm^2
   iii) lumbar malformations (local inflammation, lumbar osteosynthesis material, meningocoele, tethered cord)
3) contraindications to intrathecal morphine:
   i) chronic opioid or substance abuse (>1 month daily use)
   ii) allergy to amide local anaesthetics, morphine, or both

Sample size calculation

Based on the observational data of Koning and colleagues,[9] we assume an incidence of delirium of 19% (95% CI: 16–23%) for the group with intrathecal bupivacaine (SA) and 6% (95% CI: 2–23%) for the group with intrathecal bupivacaine and morphine (SIM). We consider an incidence of delirium of 9% in the SIM group (absolute reduction of 10%) as a clinically relevant reduction. Using an independent sample, exact-test, with an alpha of 0.05, a power of 0.80, and a 1:1 allocation ratio, a total sample size of 330 was calculated. Thirty-four patients (10%) will be added to allow for missing data and protocol violations. This will lead to two groups of 182.

Because the incidence of delirium varies between institutions, the assumption that the data of Koning and colleagues[9] are transferable to our hospital is questionable. An independent monitor will oversee the study and will perform a second sample size calculation after 200 patients have been recruited. Only the incidence of patients with delirium in the SA group will be used for the sample size calculation and we will consider an absolute reduction of 10% or a relative reduction of 0.66 clinically relevant for this sample size calculation. The smallest sample size will be chosen from the two calculations for practical reasons.

For the substudy with NFL measurements, we performed a power analysis based on the results of the study of Halaas and colleagues.[15] To detect a difference in NFL concentration between control (mean 137, standard deviation pg ml^{-1}) and intervention (mean 80, 60 pg ml^{-1}) with an alpha of 0.05 and a power of 0.95, a sample of 30 patients per group is necessary. To allow for missing data, we plan to recruit a total of 80 patients to this substudy.

Patient management

The schedule of enrolment, interventions, and assessments is summarised in Table 1.

Investigational product

The intervention is an intrathecal injection of morphine 100 μg. This will be combined with the intrathecal injection of bupivacaine10 mg for spinal anaesthesia. To prevent inadvertent dilution errors,[16] the pharmacy department will produce ready-to-use-ampules of 5 ml of bupivacaine 2.5 mg ml^{-1} and morphine 25 μg ml^{-1}. Four millilitres will be administered. The control group will receive an intrathecal injection of bupivacaine 10 mg only for spinal anaesthesia. To have the same volume and concentration, 5 ml ready-to-use-ampules of bupivacaine 2.5 mg ml^{-1} will be prepared by the pharmacy department, and 4 ml will be administered. There will be routine testing for quality (such as sterility and dose) of the solutions prepared by the pharmacy department. The

Table 1 Schedule of enrolment, interventions, and assessments of this trial. Day 0 is the day of surgery. DOS, Delirium Observation Screening.

	Enrolment and allocation	Monitoring period			Close-out
TIMEPOINT	Day -2-0	*Day 0*	*Day 1*	*Day 2*	*hospital discharge or +30 days*
ENROLMENT:					
Eligibility screen if scheduled for surgery	X				
Informed consent before surgery	X				
Day of surgery	0				
Baseline *characteristics*	x				
INTERVENTION:					
Intrathecal bupivacaine 10mg		x			
Intrathecal bupivacaine 10mg & morphine 100mcg		x			
Serum sample Neurofilament light (80 patients)		X		x	
Quality of recovery 15			x		
ASSESSMENTS:					
Baseline characteristics	x				
Delirium	←	—	—	—	→ X
DOS scores	←	—	—	—	→ X
Verbal or visual Analgesia Scores	←	—	—	—	→ X
Opiate use	←	—	—	—	→ X
30 day mortality	←	—	—	—	→ X
Serious adverse events	←	—	—	—	→ X

medication is isotonic and sterile and has a pH of 4.0, which makes it appropriate for intrathecal administration.

Perioperative management

Both groups will receive regional nerve blocks (fascia iliaca compartment block [pertrochanteric fractures] or pericapsular nerve group block [median column fractures]) as soon as possible after the fracture is diagnosed. Surgical repair is usually scheduled within 24 h, with the exact timing determined by the attending trauma surgeon and anaesthesiologist.

Before patients are positioned for the spinal injection, if needed, they will be sedated with propofol and esketamine 10–15 mg. Propofol sedation will be continued during surgery if needed, titrated to entropy monitoring (targeted value 60–80). All patients will receive dexamethasone 4 mg and ondansetron 4 mg to decrease potential side-effects, such as pruritus and nausea.

The postoperative analgesic regimen consists of paracetamol 1000 mg (four times a day) and metamizole 1000 mg (three times a day) if there is no contraindication. Contraindications include an allergy to metamizole, acute kidney injury (defined by a 20% increase in serum creatinine level or a chronic decreased glomerular filtration rate of <30 ml min^{-1}) and oxycodone 5 mg (up to 6 times a day) as needed. In addition, in the post-anaesthesia care unit (PACU), morphine or piritramide will be titrated if required to achieve satisfactory analgesia.

During the first postoperative day, analgesia is prescribed as above, and ondansetron 4 mg (three times a day) will be continued to decrease pruritus and nausea. If additional treatment for pruritus or nausea is necessary, patients can receive an extra dose of ondansetron 4 mg (if there are no contraindications) as second-line treatment. On the night of surgery, patients in both treatment arms will not be allowed to use long-acting opioids or benzodiazepines because of the interaction with the intrathecal morphine, which may lead to respiratory depression.

Standard anti-delirium precautions are taken during hospital admission. Precautions include enhancing day–night

rhythm, providing orientation materials (such as clocks, calendars, and familiar objects), stimulating family involvement, and providing sensory aids if needed. In addition, patients with preoperative cognitive impairment will receive prophylactic haloperidol 1 mg daily for 3 days.

Escape medication

For pain: i.v. morphine or i.v. piritramide during the PACU stay, with oral oxycodone, 5 mg as needed, on the ward.

For nausea or pruritus: ondansetron 4 mg as needed three times a day. On the PACU incremental doses of propofol (30 mg) or naloxone will be available if needed.

For delirium with symptoms of agitation: haloperidol 1 mg in the morning and 1.5 mg in the evening will be prescribed at the discretion of the consultant geriatrician.

Primary outcome

The incidence of delirium during hospital admission, as defined by the DSM-5 classification.

Secondary outcomes

- Delirium Observation Screening Scale (DOSS) scores (three times daily)
- pain scores on a numeric rating scale (NRS)
- postoperative opioid consumption (mg) during hospital admission transformed to morphine equivalents
- postoperative consumption (mg) of ondansetron for nausea or pruritus
- a patient questionnaire with the Quality of Recovery-15 on POD 1 (including subscales)
- pruritus severity score on POD 1
- time of mobilisation after surgery
- occurrence of complications such as infections, cerebrovascular disorders, respiratory insufficiency, and myocardial injury
- mortality
- discharge location (i.e. home, rehabilitation facility, or nursing home)
- length of hospital stay

Tertiary outcomes

Serum concentration of NFL on the second postoperative day and the increase in serum NFL concentration compared with baseline in the subset of 80 patients. NFL concentration will be measured using commercially available kits on the Simoa technology on an HD-X system (Quanterix, Billerica, MA, USA). The analysis will be performed within one batch of reagents and blinded for the clinical outcomes.

Other study variables

Baseline values which will be collected and for which the primary outcome is corrected are:

- pre-existing cognitive impairment (as scored by a questionnaire in the emergency department or known dementia)
- ASA classification
- pre-existing residential facility
- age
- body mass index (BMI)
- sex
- time from emergency department until surgery (h)
- the presence of comorbidities associated with the fracture (e.g. infections, acute kidney injury, anaemia, cardiac failure)
- type of surgical correction (hemiarthroplasty, total arthroplasty, or internal fixation)
- estimated blood loss (ml) during surgery

Data management

Data will be recorded into a Good Clinical Practice-compliant database (Castor EDC).

For data quality, the data will be reviewed by an independent monitor. Data will be available upon reasonable request after the publication of the main results.

Statistical analysis

Primary study outcome

Delirium will be analysed as a dichotomous variable using Fisher's exact test and presented as *n* (%). The primary outcome will not be corrected for multiple analyses. Logistic regression analysis is planned to correct the primary outcome for possible confounders in baseline characteristics. However, this will only be performed if a significant variance in baseline characteristics is observed. Potential confounders are known risk factors for delirium, such as age, gender, type of surgery, ASA classification, and pre-existing cognitive impairment, or factors unequally distributed over the randomisation groups based on coincidence.

An intention-to-treat analysis (primary analysis) and a per-protocol analysis (secondary analysis) will be performed.

Missing data will not be substituted.

Secondary outcomes

The continuous secondary outcomes will be analysed using the Mann–Whitney *U*-test. Categorical data will be analysed using Fisher's exact test. Repeated measures analysis of variance (ANOVA) will be used for DOSS scores, and a Bonferroni correction will be applied for secondary outcomes. Data will be presented as median (inter-quartile range [IQR]) for continuous variables and *n* (%) for categorical data.

Interim analysis

The interim analysis will be performed after $n=200$. The analysis will constitute only the incidence of delirium and mortality between groups, using Fisher's exact test. The investigators will perform the interim analysis. The independent party that stores the randomisation code will only provide the code after all the data are collected for these patients and only these patients. The independent monitor attached to this study will also oversee this process. The interim analysis of the incidence of delirium shall be used to adjust the sample size calculation. The study will be prematurely terminated if an absolute increased incidence of mortality of 5% in the intervention group is observed or the total decrease in the incidence of delirium is <5%.

Discussion

The pathogenesis of delirium is not fully understood, but multiple factors seem to be associated with its occurrence.

Well-known risk factors are age, gender, frailty, cognitive impairment, pain, and analgesic drugs. Our patients receive a regional anaesthetic block, with care and close observation by a geriatric team on a specialised ward for geriatric trauma patients. We decided against making this a multicentre trial because standard operating procedures differ from those in neighbouring hospitals and logistical challenges complicate exporting our locally produced mixture of bupivacaine/morphine to other hospitals. This decision may, however, limit the generalisability of our findings.

The main risk of the study intervention is respiratory depression from an inadvertent overdose of intrathecal morphine[17] or the co-administration of benzodiazepines or long-acting opioids on the night after surgery. The risk of inadvertent overdose is mitigated by using pre-prepared ampoules with a total dose of morphine of 125 μg. The dose remains within the therapeutic range even if an entire ampoule is administered. To administer a dangerously high dose (>300 μg), one would have to administer three ampoules, which is unlikely to occur by mistake. The co-administration of routinely administered long-acting opioids is prohibited by the study protocol. The standard postoperative analgesic regimen in our hospital does not include long-acting opioids. Benzodiazepines are prohibited on the night of the surgery. Patients that chronically use these medications will be excluded from the study. Anaesthesiologists, ward physicians, and nurses will be educated regarding interactions with intrathecal morphine. In the electronic patient file, a warning will be displayed.

The effectiveness of these measures will be monitored. Although co-administration of benzodiazepines and long-acting systemic opioids with intrathecal morphine increases the risk of late respiratory depression, the absolute risk remains very low. Indeed, the risk for respiratory depression is likely similar between systemic opioids (control group and routine practice) and low-dose intrathecal opioids (intervention group) and we therefore consider it acceptable.

The Salmon-Mind study is the first large randomised, controlled trial of the effect of intrathecal morphine on the incidence of delirium in patients undergoing a repair of proximal femur fracture. We will correlate changes in NFL concentration to delirium occurrence. We would like to see if intrathecal morphine, an inexpensive addition to bupivacaine, could reduce the incidence of delirium with limited side-effects.

Dissemination plans

The data collected will not be used to license or register any pharmaceuticals. Data from the research will be made available to the scientific community promptly and responsibly. All named co-authors agreed to participate in producing a detailed scientific report, which will be submitted to a widely accessible scientific journal. Authorship of the final paper(s), interim publications, or abstracts will be decided according to active participation in the design, writing, and statistical analysis. Contributing or participating investigators will be acknowledged in the final paper.

Authors' contributions

Study protocol design: AT, MK, SK
Drafting of paper: all authors
Subsequent revising of paper: all authors

Declarations of interest

The authors declare that they have no conflicts of interest.

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